FENS Regional Meeting

Belgrade, Serbia, July 10–13, 2019

ДНС SNS Друштво за неуронауке Србије Serbian Neuroscience Society

National Neuroscience Society of Romania

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Abstract Book

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Editor: Andjelka Isakovic

Associate Editor: Sonja Misirlic Dencic

Assistant Editors: Tatjana Nikolic, Milica Velimirovic Bogosavljevic

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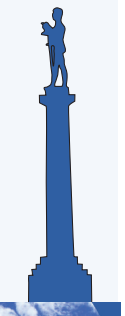

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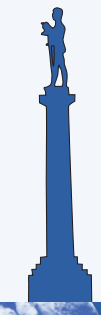

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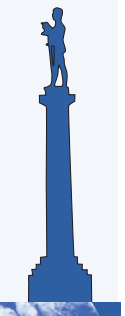

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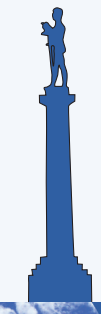

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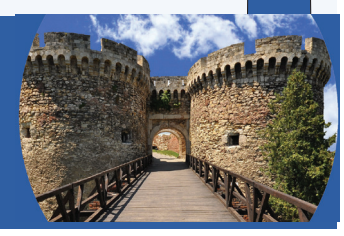

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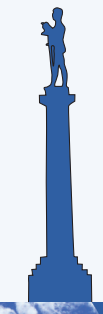

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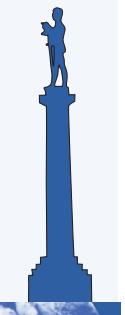

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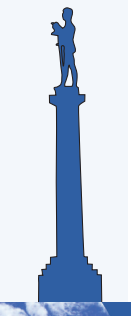

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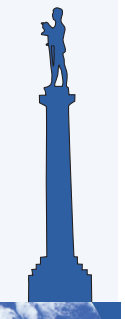

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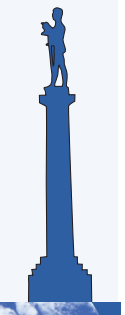

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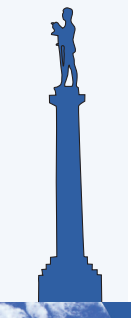

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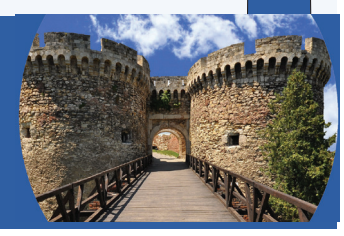


Wednesday, July 10, 2019

18:00-19:00

Room Pacific

PLENARY LECTURES

OPENING LECTURE

Chair: Carmen Sandi

GENOMICS OF AD AND OTHER NEURODEGENERATIVE DISEASES

John Hardy

UK Dementia Research Institute at UCL Queen Square Institute of Neurology, Department of Neurodegenerative Diseases & Reta Lila Weston Laboratories, London, United Kingdom

Genetic analyses of the common neurodegenerative diseases are revealing many loci for each of them, and point to approaches in management. For example, the association of APP with Alzheimer's disease and the subsequent development Amyloid hypotheses are the foundation for the many Alzheimer's disease trials. The recent failures of targeting amyloid in Alzheimer's disease treatment prompt second thoughts on the approach, including but not limited to case selection and timing of treatment.

Based on the findings of multiple genetic loci in recent past, researchers using other omics and bioinformatics are now starting to put together the jigsaw. This explosion of information begins to reveal commonalities on the loci involved in each disease entity. These are for Alzheimer's disease, amyloid induced neuronal damage, for typical Parkinson's disease, lysosomes and autophagic clearance, for early onset Parkinson's disease, mitophagy, for fronto-temporal dementia / amyotrophic lateral sclerosis, the ubiquitin proteasome, and for the pure amyotrophic lateral sclerosis, the stress granule response.

This idea of a failing damage response will hopefully begin to enable links to be drawn between the genetic, transcriptomics, biomarkers and pathogenesis of the diseases. Coupled with other clinical information and epidemiological assessments of risk factors for the diseases, these will provide new angles in the management of neurodegenerative diseases.

Saturday, July 13, 2019

16:20-17:20

Room Pacific

PLENARY LECTURES

CLOSING LECTURE

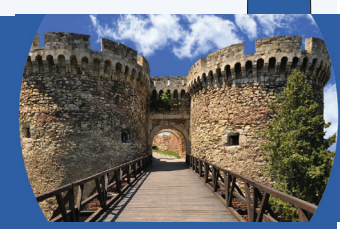
Chair: Carmen Sandi/Bayram Yilmaz

THE MAKING AND KEEPING OF MEMORY

Richard GM Morris

The University of Edinburgh, Edinburgh, UK

Understanding the neurobiology of memory is recognised as one of the grand challenges of contemporary neuroscience. It is a problem to be approached from multiple levels of analysis - from 'top-down' in recognising the several qualitatively different types of memory and their brain imaging correlates, through to 'bottom-up' approaches reflecting likely conserved and newly evolved molecular mechanisms of neuronal plasticity. I shall begin with a focus on the neurophysiology of the 'making' of memory (encoding) and describe recent research using rodents (rats) which supports the involvement of activity-dependent synaptic plasticity in memory trace formation, but calls into question whether postsynaptic cell firing is always required (Rossato et al, *Current Biology,* 2018). I shall then turn to the 'keeping' of memory (consolidation) with a focus on one specific aspect of memory retention. This derives from the 'synaptic tagging and capture' model of protein synthesis-dependent long-term potentiation (Frey and Morris, *Nature* 1997) which asserts that, as much memory encoding is automatic, there must be selectivity to its retention to avoid saturation of the distributed networks of the hippocampus and related structures that mediate recent memory storage. This leads on to an exploration of the determinants of selectivity, including the impact of peri-event novelty in enhancing retention through its enhancement of protein synthesis. This issue has recently been explored in mice using optogenetic techniques focusing, somewhat surprisingly, on the locus coeruleus (Takeuchi et al, *Nature,* 2016).



Thursday, July 11, 2019

10:30-11:30

Room Pacific

Plenary Lectures

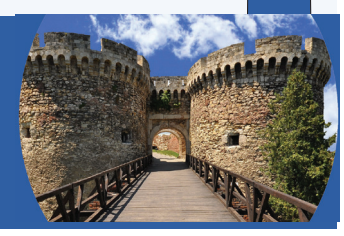
Chair: Ljubisav Rakic

BLOOD-BRAIN BARRIER AND CNS DYSFUNCTION AND PROTECTION

Berislav V. Zlokovic

Zilkha Neurogenetic Institute, Department of Physiology and Neuroscience, Keck School of Medicine, University of Southern California, Los Angeles, United States

I will discuss the cellular and molecular mechanisms underlying the link between BBB dysfunction and CNS dysfunction, and protection. Examples will include the roles of brain endothelial *MSFD2a*, *LRP1*, and *GLUT1* gene in maintaining the BBB integrity and normal neuronal structure function, and genetic defects in vascular cells contributing to rare monogenic human neurological disorders. Next, will discuss human Alzheimer's *PICALM* mutations, and their effects on Abeta BBB clearance. Then, will examine our recent neuroimaging and CSF findings indicating that BBB breakdown is an independent early biomarker of human cognitive dysfunction. Then, will briefly review our findings in pericyte-deficient models including pericyte-specific ablation model causing rapid loss of neurons caused by circulatory failure and loss of pericyte-derived neurotrophic factor, pleiotrophin. Then will turn to neurodegeneration therapeutic approaches targeting vascular cells including endothelial-specific AAV2-BR1-mediated delivery of *LRP1* minigene and inhibition of the proinflammatory cyclophilin A (CypA)-MMP9 pathway, and early attempts with iPSC-derived human pericytes to improve BBB integrity and Ab and tau clearance. Finally, I will discuss treatment of stroke with 3K3A-activated protein C (APC), a BBB stabilizing, anti-inflammatory protease that has successfully completed Phase 2a trial in stroke patients. I will show our recent findings on 3K3A-APC-mediated post-ischemic brain regeneration and formation of functional mouse-human hybrid neuronal circuits with human-derived neural stem cells, and 3K3A-APC treatments for white matter stroke, ALS (mouse model and human iPSC-derived C9 motor neuron ALS model), and effects in a mouse model of AD. Potential and applications for human trials will be discussed.



Thursday, July 11, 2019

15:10-16:10

Room Pacific

PLENARY LECTURES

Chair: Mihai Moldovan

GENE DELIVERY ACROSS THE BLOOD-BRAIN-BARRIER, WHOLE-BODY TISSUE CLEARING, AND OPTOGENETICS TO UNDERSTAND AND INFLUENCE PHYSIOLOGY AND BEHAVIOR

Viviana Gradinaru

Molecular and Cellular Neuroscience Center of the Chen Institute, California Institute of Technology CALTECH, Pasadena, CA, United States

Our research group at Caltech develops and employs optogenetics, tissue clearing, and viral vectors to gain new insights on circuits underlying locomotion, reward, and sleep. In most recent work the group has delineated novel arousal-promoting dopaminergic circuits that might be at the root of sleep disturbances common to numerous neuropsychiatric disorders (Cho et al., Neuron, 2017). Present-day neuroscience relies on genetically-encoded tools; in both transgenic and non-transgenic animals, current practice for vector delivery is stereotaxic brain surgery—an invasive method that can cause hemorrhages and non-uniform expression over a limited volume. To address this limitation, we have developed viral-vector selection methods to identify engineered capsids capable of reaching target cell-populations across the body and brain after noninvasive systemic delivery (Deverman et al, Nature Biotechnology, 2016). We use whole-body tissue clearing to facilitate transduction maps of systemically delivered genes (Yang et al, Cell, 2014; Treweek et al, Nature Protocols, 2016). With novel AAV capsids, we achieved brain-wide transduction in adult mice after systemic delivery and sparse stochastic Golgi-like genetic labeling that enables morphology tracing for both central and peripheral neurons (Chan et al, Nature Neuroscience, 2017). Viral vectors that can efficiently and selectively deliver transgenes to target tissues after injection into the bloodstream allow us to genetically modify a high percentage of desired cells with more homogeneous coverage, without the need for either highly invasive direct injections or time-consuming transgenesis. Since CNS disorders are notoriously challenging due to the restrictive nature of the blood brain barrier, the recombinant vectors engineered to overcome this barrier can enable potential future use of exciting advances in gene editing via the CRISPR-Cas, RNA interference and gene replacement strategies to restore diseased CNS circuits.

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Thursday, July 11, 2019

18:10-19:10

Room Pacific

Plenary Lectures

Chair: Gulgun Sengul

BRAIN & MIND: WHO IS THE PUPPET AND WHO THE PUPPETEER?

George Paxinos

University of New South Wales, Australia

After presenting some of what he learned through his journey in the brain, the speaker will address the question in the title, a question with social, legal and religious implications. If the mind controls the brain, then there is FREE WILL and its corollaries, dignity and responsibility. You are king in your skull-sized kingdom. You are the architect of your destiny. If, on the other hand, the brain controls the mind, an incendiary conclusion follows: There can be no FREE WILL, no praise, no punishment and no purgatory. Our brain is the riverbed that holds and channels our stream of consciousness (Koch, 2012). It is molded by the family and the culture we are raised in. Experience sculpts out our character from the genetic material we are granted as Phidias sculpted Apollo from a block of Parian marble. Alzheimer's disease will pay an unwelcome visit to many of us at the end of life. It will disrupt the internal structure of our neurons and we will be living evidence the mind is the product of the brain and has no influence on it. Which one of us would not like to discard our depression, anxieties, obsessions, compulsions, our unrequited love? If only the puppet could get hold of one of the strings with which the brain makes it dance. It seems the puppet is free only in as much as it loves its strings (Harris, 2012).

Friday, July 12, 2019

10:30-11:30

Room Pacific

Plenary Lectures

Chair: Jelena Radulovic

GAMMA FREQUENCY ENTRAINMENT USING SENSORY STIMULI CONFERS NEUROPROTECTION AND ENHANCES COGNITIVE FUNCTION

Li-Huei Tsai

Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA, United States

Rhythmic neural activity in the gamma range (30-80 Hz) is modulated during various aspects of cognitive function and has been shown to be disrupted in several neurological conditions, including Alzheimer's disease (AD). Impaired gamma oscillations have also been reported in several AD mouse models, even before the onset of Aβ accumulation and major cognitive impairment. It is well established that local network oscillations at specific frequencies can be induced in cortical areas using sensory stimuli. Recently, we applied this approach, which we term Gamma ENtrainment Using Sensory stimuli (GENUS), using a light programmed to flicker at 40 Hz to induce gamma oscillations in the visual cortex of AD model mice. We found a profound reduction in amyloid load in visual cortex after 1 hr of visual GENUS that appears to involve the concerted actions of many different cell types, including neurons and microglia to reduce the production and enhance clearance of Aβ, respectively. Chronic exposure to GENUS reduced amyloid plaque and phosphorylated Tau pathology in multiple brain regions in 5XFAD and P301S transgenic mice, respectively, and improved learning and memory. Therefore, GENUS represents a novel and powerful non-invasive approach to combat AD related pathology and symptoms. We are currently testing GENUS in human subjects to determine it's utility in tackling human neurological disorder.

Friday, July 12, 2019

15:10-16:10

Room Pacific

PLENARY LECTURES

Chair: Ana-Maria Zagrean

ASSEMBLING TRIDIMENSIONAL BRAIN MODELS TO STUDY HUMAN DEVELOPMENT AND DISEASE

Sergiu P Pasca

Stanford University, Stanford, CA, United States

Progress in dissecting the molecular programs underlying human brain development and in understanding neuropsychiatric disorders has been remarkably slow. This is partly due to lack of access to functioning human brain tissue, translating findings in rodent models and unavailability of functionally relevant in vitro models. In my talk, I will describe efforts in my laboratory to derive 3D brain region-specific cultures starting from human pluripotent stem cells. Specifically, I will show how to derive 3D organoids resembling either the dorsal forebrain and containing cortical glutamatergic neurons, or ventral forebrain and containing GABAergic neurons. These subdomain-specific forebrain organoids can be fused in vitro to generate assembloids and recapitulate the saltatory migration of interneurons and to generate functional circuits of the human cerebral cortex. I will also describe work on human gliogenesis and maturation in over 20+ month-long cultures. Lastly, I will demonstrate how our modular 3D platform can be used to model disease and to study the role of voltage gated calcium channels and the consequences of mutations associated with neuropsychiatric disorders.

Friday, July 12, 2019

18:10-19:10

Room Pacific

Plenary Lectures

Chair: Emel Ulupinar

SOMATOSENSORY CIRCUIT ALTERATIONS IN NEURODEVELOPMENTAL DISORDERS

Reha Erzurumlu

Department of Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, MD, United States

We have been investigating the development and plasticity of the trigeminal sensory pathway in mouse models of various genetic defects that alter brain development. Two mouse models with deletion of genes associated with autism spectrum disorders (ASD) and Rett syndrome (RTT) show altered somatosensory cortical phenotypes that could be related to children with ASD and RTT with distinct tactile sensitivities. MET receptor tyrosine kinase is activated by hepatocyte growth factor (HGF) and both are expressed in the developing brain. MET regulates neurogenesis, differentiation, migration, connectivity, and synaptic plasticity. Mutations in *MET* gene are identified as a risk factor for ASD. Mutations in the methyl-CpG-binding protein 2 (*MECP2*) gene have been linked to RTT. We studied thalamocortical synaptic transmission in the whisker-barrel cortex of mice with genetically impaired Mecp2 or Met function. Whole cell recordings from layer IV neurons revealed that in *Mecp2* null mice there is an excitation/inhibition (E/I) imbalance, biased toward inhibition, due to an increase in efficacy of postsynaptic $GABA_A$ receptors. Enhanced inhibition impairs the transmission of tonic sensory signals from the thalamus to the somatosensory cortex, a mechanism that could account for hypo tactile sensitivity. We also investigated somatosensory thalamocortical synaptic communication in mice deficient in Met activity. The E/I ratio dramatically increased due to decreased postsynaptic $GABA_A$ receptor-mediated inhibition in mice lacking active Met in the cerebral cortex. This mechanism could account for tactile hypersensitivity, commonly seen in children with ASD. Additionally, in contrast to wild-type mice, insulin failed to increase $GABA_A$ receptor-mediated response in the primary somatic sensory cortex of mice with compromised Met signaling. Insulin resistance of $GABA_A$ receptor-mediated response in *Met* mutant mice most likely results from desensitized insulin receptors. Lastly, we have been examining the cortical connectivity patterns in mice with a prominent axon guidance defect in the brainstem that leads to bilateral whisker representations in the thalamus and cortex. This mouse model allows for investigating cortical wiring rules when thalamocortical axons bring in a bilateral face and whisker representations to the cortex.

Research in the Erzurumlu laboratory is supported by NIH/NINDS grants R01NS04818 and R01NS092216.

Saturday, July 13, 2019

10:30-11:30

Room Pacific

PLENARY LECTURES

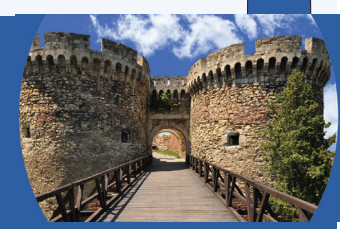
Chair: Selma Kanazir

CELL TYPES OF ADULT MOUSE CORTEX AND HIPPOCAMPUS

Bosiljka Tasic

Allen Institute for Brain Science, Seattle, WA, United States

Defining cell types that constitute the brain is a critical step towards understanding the relationship between brain structure and function. We are building a state-of-the-art single-cell transcriptomic atlas of adult male and female mouse brains by employing standardized experimental and computational pipelines. I will present a joint analysis of cortical and hippocampal areas based on more than 1 million single cell transcriptomes derived by two experimental platforms. As we reported previously, most GABAergic cell types are shared among cortical areas, whereas glutamatergic types show regional specificity. However, hippocampal GABAergic neurons show distinct gene expression signatures, and glutamatergic neurons in some neighboring cortical regions show gene expression differences that present themselves as continua. I will present new approaches that utilize single cell transcriptomic and epigenomic information to enable genetic access to cell types and classes for investigating their function.



Wednesday, July 11, 2019

8:30–10:10

Room Pacific

Symposium 01

Cellular signaling and quality control mechanisms in neurodegeneration

Organizers: Simone Engelender (Haifa, IL) and Tiago Outeiro (Waldweg, DE)

ROLE OF MONOUBIQUITINATION AND SUMOYLATION IN THE HOMEOSTASIS OF ALPHA-SYNUCLEIN IN PARKINSON'S DISEASE

S. Engelender

The B. Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

simone@technion.ac.il

Parkinson's disease (PD) is characterized by the neuronal accumulation of a-synuclein, and prominent death of dopaminergic neurons in the substantia nigra. At post-mortem examination, nigral neurons of PD patients contain significant amount of Lewy bodies composed of aggregated a-synuclein. Although the presence of Lewy bodies are correlated with PD, the mechanisms responsible for its accumulation and aggregation in the disease have remained elusive. We have shown that monoubiquitination by SIAH ubiquitin-ligase promotes the proteasomal degradation of a-synuclein. This monoubiquitination is dynamic, and it is constantly deubiquitinated by the deubiquitinase USP9X. When not properly degraded by the proteasome, monoubiquitinated a-synuclein form toxic aggregates. As age is one of the main risk factors for PD and proteasomal activity decreases with aging, it is possible that the accumulation of monoubiquitinated a-synuclein may play a role in the aggregation of a-synuclein in PD. More recently, we found that the degradation and aggregation of a-synuclein are regulated by another post-translational modification, SUMOylation. We found that PIAS2 is a SUMO-ligase for a-synuclein. SUMOylation by PIAS2 decreases a-synuclein monoubiquitination, causing a decrease in the proteasomal degradation of a-synuclein and triggering its accumulation. SUMOylation by PIAS2 also directly promotes the aggregation of a-synuclein. Importantly, a-synuclein disease mutants are more readily SUMOylated than wild type a-synuclein, suggesting the possibility that SUMOylation could contribute to the pathogenesis of familial PD with a-synuclein mutations. Still supporting a more widespread role of SUMOylation in the disease, the levels of SUMOylated a-synuclein and PIAS2 are increased in sporadic PD brains. Therefore, we propose that SUMOylation may lead to the accumulation and aggregation of a-synuclein in sporadic disease as well. Inhibition of a-synuclein SUMOylation may help prevent the accumulation of pathological a-synuclein in PD.

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POSTTRANSLATIONAL MODIFICATIONS AS REGULATORS OF ALPHA-SYNUCLEIN HOMEOSTASIS

Tiago Fleming Outeiro

Department of Epxerimental Neurodegeneration, University Medical Center Goettingen, Goettingen, Germany

touteiro@gmail.com

The aggregation of alpha-synuclein (ASYN) in Lewy bodies and Lewy neurites is the typical pathological hallmark of Parkinson's disease (PD) and other synucleinopathies. Furthermore, mutations in the gene encoding for ASYN are associated with familial and sporadic forms of PD, suggesting this protein plays a central role in the disease. However, the precise contribution of ASYN to neuronal dysfunction and death is still unclear. There is intense debate on the nature of the toxic species of ASYN, and little is still known about the molecular determinants of oligomerization and aggregation of ASYN in the cell. By taking advantage of studies in model organisms, we are investigating the effect of various posttranslational modifications on the toxicity and aggregation of ASYN. We found that glycation and acetylation are emerging as important modifications affecting ASYN aggregation. In addition, we are also defining the molecular mechanisms triggered by extracellular forms of ASYN, a process associated with the spreading of pathology. In total, our data shed light into the molecular underpinnings of synucleinopathies, opening novel perspectives for future therapeutic interventions.

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THE ASSOCIATION OF LYSOSOMAL DYSFUNCTION TO NEURODEGENERATION: FOCUS ON SYNUCLEINOPATHIES

Maria Xilouri, Nikos Papagiannakis, Leonidas Stefanis

Biomedical Research Foundation of the Academy of Athens; Medical School of the National and Kapodistrian University of Athens, Athens, Greece

lstefanis@bioacademy.gr

Synucleinopathies represent a group of neurodegenerative diseases, such as Parkinson's disease (PD), Dementia with Lewy Bodies and Multiple System Atrophy, characterized by the aberrant deposition of alpha-synuclein (AS) in the nervous system of affected individuals. Increasing genetic, neuropathological and experimental data implicate the lysosomes in the pathogenesis of these diseases, largely through altered metabolism of AS. Dysfunction of lysosomal, and in particular autophagic, pathways is thought to be related to the accumulation of aberrant AS conformations. A case in point is the genetic subtype of PD linked to mutations in the GBA1 gene, in which case it is thought that the partial enzyme deficiency of the encoded Glucocerebrocidase gene leads to reduced lysosomal clearance of AS. In our lab, we have focused on the selective autophagic pathway of Chaperone-Mediated Autophagy (CMA). We have provided evidence that downregulation of CMA through molecular inhibition of the transmembrane lysosomal receptor Lamp2a, the rate-limiting step in the pathway, leads to aberrant AS accumulation in neuronal cell cultures and in vivo, while at the same time it induces profound neurodegeneration of the nigrostriatal axis (Xilouri et al., 2016). On the flip side, we have demonstrated that molecular enhancement of CMA through the converse strategy, Lamp2a overexpression, leads to neuroprotection against AS-mediated neurotoxicity in the nigrostriatal axis, while also reducing AS levels (Xilouri et al., 2013). More recent data, based on biomarker studies in patients, suggest that in fact CMA and, more broadly, lysosomal dysfunction, may be a systemic feature of PD.

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Organizers: Simone Engelender (Haifa, IL) and Tiago Outeiro (Waldweg, DE)

ROLE OF LRRK2 PHOSPHORYLATION IN PARKINSON'S DISEASE-ASSOCIATED NEURODEGENERATION

Alice Biosa[1], Evy Lobbestael[2], Alice Kaganovich[3], Susanna Cogo[1], Laura Civiero[1], Mark Cookson[3], Veerle Baekelandt[2] and Elisa Greggio[1]

[1]Department of Biology, University of Padova, Padua, Italy;
[2]Department of Neurosciences, KU Leuven, Leuven, Belgium;
[3]Laboratory of Neurogenetics, NIA, NIH, Bethesda, Maryland, USA

elisa.greggio@unipd.it

Mutations in the Leucine-rich repeat kinase 2 (*LRRK2*) cause autosomal dominant, late onset Parkinson's disease (PD) and common variants at the *LRRK2* locus predispose to sporadic disease. Although the role of LRRK2 in PD is well-established, the molecular mechanisms behind LRRK2-linked pathology are still unclear. LRRK2 is a multidomain protein with dual kinase-GTPase activity with mutant LRRK2 resulting in gain of kinase function. Being associated with multiple signal transduction pathways, LRRK2 phosphorylates specific substrates, but it is also the target of kinases and phosphatases. Specifically, LRRK2 is phosphorylated within a cluster of serine residues (Ser910/935) which are important to control LRRK2 subcellular localization via binding with 14-3-3 proteins. Of interest, LRRK2 kinase inhibitors as well as LRRK2 pathogenic mutations result in dephosphorylation of Ser910/935 raising a question as to whether dephosphorylated LRRK2 is pathogenic or protective. We recently identified the kinase PAK6 as an interactor of the GTPase domain of LRRK2. Functionally, PAK6 controls the phosphorylation state of LRRK2 by a novel mechanism: PAK6 binds and phosphorylates 14-3-3γ at Ser59 and this phosphorylation serves as a switch to dissociate 14-3-3 from LRRK2, resulting in Ser935 dephosphorylation and LRRK2 subcellular relocalization. Of relevance for PD, 1) PAK6 autophosphorylation is deregulated in mutant LRRK2 mouse brains and 2) PAK6 rescues mutant LRRK2-associated neurite shortening through phosphorylation of 14-3-3γ, overall suggesting that PAK6-dependent LRRK2 dephosphorylation is protective, similar to the effect of LRRK2 inhibition. We are currently assessing the putative protective role of PAK6 kinase activity in vivo in PD mouse models.

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Symposium 02

Neurobiological mechanisms for susceptibility and resilience: "yin and yang" or "apples and oranges"?

Organizers: Dani Dumitriu (New York, NY, USA)

CHRONIC CHEMOGENETIC ACTIVATION OF FOREBRAIN EXCITATORY NEURONS IN POSTNATAL LIFE EVOKES LONG-LASTING BEHAVIORAL CHANGES

Sthitapranjya Pati[1], Kamal Saba[2], Sonali S Salvi[1], Praachi Tiwari[1], Sourish Mukhopadhyay[1], Toshali Banerjee[1], Pratik Chaudhari[1], James P Clement[3], Anant B Patel[2], Vidita A Vaidya[1]

[1]Department of Biological Sciences, Tata Institute of Fundamental Research, Mumbai, Maharashtra, India;
[2]NMR Microimaging and Spectroscopy, Centre for Cellular and Molecular Biology, Hyderabad, Telangana, India;
[3]Neuroscience Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, Karnataka, India

sthitapati@tifr.res.in

The first few weeks after birth, mark the critical period wherein circuits are tuned to external stimuli and are particularly amenable to modification by the environment (Hensch, 2005; Koenig et al., 2011)this activity-dependent development is triggered by the functional maturation of local inhibitory connections and driven by a specific, late-developing subset of interneurons. Ultimately, the structural consolidation of competing sensory inputs is mediated by a proteolytic reorganization of the extracellular matrix that occurs only during the critical period. The reactivation of this process, and subsequent recovery of function in conditions such as amblyopia, can now be studied with realistic circuit models that might generalize across systems.", "author" : [{ "dropping-particle" : "", "family" : "Hensch", "given" : "Takao K", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Nature reviews. Neuroscience", "id" : "ITEM-1", "issue" : "11", "issued" : { "date-parts" : [["2005"]] }, "page" : "877-88", "title" : "Critical period plasticity in local cortical circuits.", "type" : "article-journal", "volume" : "6" }, "uris" : ["http://www.mendeley.com/documents/?uuid=ffc829c1-5dd9-4db7-81ea-5a781662532b"] }, { "id" : "ITEM-2", "itemData" : { "DOI" : "10.3109/10253890.2011.604879", "ISSN" : "1025-3890", "PMID" : "21848435", "abstract" : "Stress is a known precipitant for metabolic and neurological diseases, with sensitive periods identified across the developmental continuum from conception to old age. However, the effects of stress may vary depending on the point or points along the developmental trajectory when adversity strikes. Past research has emphasized the consequences of stress on fully developed physiological systems in the brain and periphery, but more recent studies have explored the impact of stress on systems at different stages of maturation, with differential effects being revealed. This review provides an overview of the diverse effects of stress at critical developmental stages and the potential outcomes that may be associated with experiencing environmental adversity during ontogeny.", "author" : [{ "dropping-particle" : "", "family" : "Koenig", "given" : "James I.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Walker", "given" : "Claire-Dominique", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Romeo", "given" : "Russell D.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Lupien", "given" : "Sonia J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Stress", "id" : "ITEM-2", "issue" : "5", "issued" : { "date-parts" : [["2011", "11", "17"]] }, "page" : "475-480", "title" : "Effects of stress across the lifespan", "type" : "article-journal", "volume" : "14" }, "uris" : ["http://www.mendeley.com/documents/?uuid=e2c82e14-076b-3833-87a6-09219a6aef3a"] }], "mendeley" : { "formattedCitation" : "(Hensch, 2005; Koenig et al., 2011. Previous work from our and other labs have shown that rodent models of early life stress show persistent increased anxiety in adulthood, in addition to enhanced serotonin 2A (5-HT_{2A}) function (Madhurima Benekareddy et al., 2010). Results from several studies also indicate that cortical 5-HT_{2A} may play a causal role in the emergence of these long-lasting changes (Madhurima Benekareddy et al., 2011; Sarkar et al., 2014, Weisstaub et al., 2006)implicated in the pathophysiology of mood and anxiety disorders, is significantly enhanced in the maternal separation model of early life stress. We examined whether postnatal 5-HT(2. The 5HT_{2A} receptor is a G-protein coupled receptor coupled to Gqα mediated signaling (N. M. Barnes & Sharp, 1999)much effort has been directed towards understanding the function attributable to individual 5-HT receptors in the brain. This has been helped, in part, by the synthesis of a number of compounds that selectively interact with individual 5-HT receptor subtypes--although some 5-HT receptors still lack any selective ligands (e.g. 5-ht1E, 5-ht5A and 5-ht5B receptors and causes neuronal depolarization (Puig et al., 2003). Coincidentally, other Gq-coupled receptors like M1/M5 muscarinic acetylcholine receptors and α1-adrenergic receptors also show altered function in animals with a history of early life stress (Proulx et al., 2014)we employed multiphoton imaging simultaneously with whole-cell electrophysiological recordings to examine potential interactions between ACh-induced Ca(2+. We hypothesized that increased activation of cortical excitatory neurons by activating Gq-mediated signaling during the postnatal critical window is sufficient to bring about persistent increase in anxiety and depressive-like behavior in adulthood. Using a chemogenetic approach, we showed that chronic activation of forebrain excitatory neurons in first two weeks of postnatal life, not in adulthood is sufficient to evoke a long-lasting increase in anxiety-like behavior and impaired sensory-motor gating in mice.

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Room Atlantic 1

Symposium 02

Neurobiological mechanisms for susceptibility and resilience: "yin and yang" or "apples and oranges"?

Organizers: Dani Dumitriu (New York, NY, USA)

EFFECT OF SOCIAL STRESS ON CIRCADIAN RHYTHMS AND SLEEP-WAKE CYCLE

He Liu[1], Basma Radwan[1], Merima Sabanovic[1,2], Gloria Jansen[1,3], Aisha Al-Hammadi[1] and Dipesh Chaudhury[1]

[1]New York University Abu Dhabi (NYUAD), Division of Science, Saadiyat Island, United Arab Emirates;
[2]Present Address: Oxford University, Welcome Trust Doctoral Training Program in Neuroscience;
[3]Present Address: Cambridge University, welcome Trust Doctoral Training Program, Department of Physiology, Development and Neuroscience$_2$

dc151@nyu.edu

Though it is known that daily rhythms are disrupted in patients suffering from mood disorders, the molecular mechanisms linking aberration in circadian / sleep rhythms and mood disorders is still not well understood. Observations that brain regions associated with mood regulation have robust neural connections, and overlapping molecular pathways, with regions that regulate biological rhythms allow us to investigate the link between these brain regions following expression of depression-like behaviour. We are using a combination of rodent behavioural model of stress together with electrophysiological and molecular approaches to investigate changes in physiological and molecular dynamics between brain regions that encode mood, circadian rhythms and sleep/wake rhythmicity in mice that are resilient (non-depressed) and susceptible (depressed) to social defeat stress.

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COGNITIVE RISK FACTORS OF VULNERABILITY TO POSTTRAUMATIC STRESS DISORDER

Eva Mikics, Laszlo Szente, Zoltan Balogh, Mano Aliczki, Zoltan Kristof Varga, Christina Miskolczi, Biborka Bruzsik, Laszlo Biro, Huba Szebik, Mate Toth

Laboratory of Translational Behavioural Neuroscience, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary

mikics.eva@koki.mta.hu

Experiencing traumatic events during which an individual faces a lethal threat or serious injury can lead to the development of posttraumatic stress disorder (PTSD), a severe psychopathological condition. Importantly, only 10-30% of trauma-exposed individuals develop PTSD progressively after a traumatic life event, while the majority of individuals recover without long-term consequences. Thus, identification of risk factors and mechanisms that increase vulnerability to PTSD represents a major clinical challenge with high potentials in prevention and therapy. Recently, individual cognitive variations have been implicated as key factors in PTSD vulnerability, however, their contributions to core symptoms, i.e. inability to extinguish traumatic memories and generalization of these fear memories to safe/neutral situations are not understood. Here we present our findings on long-term behavioral consequences of footshock exposure in an established rat model of PTSD and its correlated neuronal activation patterns upon re-exposure to the traumatic context. To identify pre-trauma cognitive vulnerabilities, we applied a complex cognitive test battery to rats before trauma exposure. 28 days after trauma, resilient and vulnerable subjects have been selected on the basis of fear generalization and extinction deficits. Random forest statistics were used to identify pre-trauma cognitive risk factors of vulnerability. Structural and plasticity-related neuronal correlates were investigated in the the prefrontal cortex (responsible for extinction deficits) and the hippocampus (safe context discrimination impairments) of vulnerable and resilient subpopulations. Our results suggest that certian cognitive factors predict PTSD vulnerability that is accompanied by placticity-related changes in the prefrontal-hippocampal-bed nucleus of stria terminalis circuitry.

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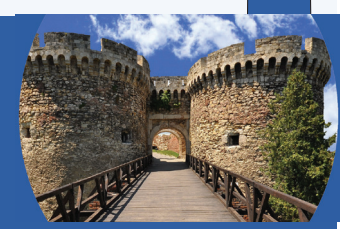

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Organizers: Dani Dumitriu (New York, NY, USA)

NEURONAL FUNCTION-STRUCTURE DIFFERENCES MEDIATING VARIABLE STRESS RESPONSES IN INBRED MICE

Dani Dumitriu

Columbia University, New York, USA

dani.dumitriu@columbia.edu

Aims: Like humans, mice display individual variability in stress-response. Some mice subjected to physical and psychosocial stress by another mouse succumb to maladaptive symptoms such as social avoidance and anhedonia. These mice are labeled "susceptible". Other mice, despite a similar stressful experience, continue to behave indistinguishably from non-stressed controls. These mice are labeled "resilient". Importantly, this individual variability is present in genetically identical (inbred) mice raised in standard conditions. This raises the interesting possibility that resilience and susceptibility result from subtle differences in patterns of neuronal connectivity. Methods: To address this, we developed an acute model of social defeat stress in which resilience and susceptibility can be determined within one hour of the stressor. This enables detailed studies of structural and functional connectivity using immediate early gene markers. Based on known involvement of the prefrontal-amygdala circuit in stress-response, we targeted this pathway with a combination of viral-mediated fluorescent labeling, immunohistochemistry, high resolution confocal imaging, and chemogenetic manipulations. Results: We found susceptibility to be associated with hyperexcitability of this pathway, as well as a difference in the morphology of individual neurons. Inhibiting this pathway during acute social defeat stress using an intersectional chemogenetic approach successfully shifted the population response toward resilience. Conclusions: Despite genetic, developmental and environmental homogeneity, inbred mice show divergent stress-responses. This behavioral dichotomy results from subtle but significant differences in the function and structure of circuits that mediate the stress-response, providing a potential target for therapeutic interventions that might prevent susceptibility in at risk individuals.

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MAPPING RESILIENCE: DISCOVERING STRUCTURE IN MESOSCALE ELECTRICAL BRAIN RECORDINGS

Rainbo Hultman[1], Kyle Ulrich[8], Benjamin D. Sachs[10], Cameron Blount[1], David E. Carlson[7], Nkemdilim Ndubuizu[1], Rosemary C. Bagot[11], Eric Parise[11], Mai-Anh T. Vu[1,2], Neil M. Gallagher[1,2], Joyce Wang[1], Alcino J. Silva[12], Karl Deisseroth[13], Stephen D. Mague[1], Marc G. Caron[4], Eric J. Nestler[11], Lawrence Carin[8], Kafui Dzirasa[1,2,3,5,6,9,14]

1Dept. of Psychiatry and Behavioral Sciences, 2Dept. of Neurobiology, 3Center for Neuroengineering, 4Dept. of Cell Biology, 5Dept. of Neurosurgery, 6Duke Institute for Brain Sciences, Duke University Medical Center, Durham, North Carolina, USA;
7Dept. of Civil and Electrical Engineering, 8Dept. of Electrical and Computer Engineering, 9Dept. of Biomedical Engineering, Duke University, Durham North Carolina, USA;
10Dept. of Psychological and Brain Sciences, Villanova University, Villanova, PA, USA. 11Fishberg, Dept. of Neuroscience, Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, New York, New York, USA, 12Depts. of Neurobiology, Psychiatry & Behavioral Sciences and Psychology, Integrative Center for Learning and Memory, Brain Research Institute, University of California, Los Angeles, California, USA. 13Depts. of Bioengineering and Psychiatry and Howard Hughes Medical Institute, Stanford University, Stanford, California, USA. 14Lead Contact.

kafui.dzirasa@duke.edu

Brain-wide fluctuations in local field potential oscillations reflect emergent network-level signals that mediate behavior. Cracking the code whereby these oscillations coordinate in time and space (spatiotemporal dynamics) to represent complex behaviors would provide fundamental insights into how the brain signals emotional pathology. Using machine learning, we discover a spatiotemporal dynamic network that predicts the emergence of major depressive disorder (MDD)-related behavioral dysfunction in mice subjected to chronic social defeat stress. Activity patterns in this network originate in prefrontal cortex and ventral striatum, relay through amygdala and ventral tegmental area, and converge in ventral hippocampus. This network is increased by acute threat, and it is also enhanced in three independent models of MDD vulnerability. Finally, we demonstrate that this vulnerability network is biologically distinct from the networks that encode dysfunction after stress. Thus, these findings reveal a convergent mechanism through which MDD vulnerability is mediated in the brain.

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Room Atlantic 2

Symposium 03

Rodent models of social behavior and emotional states as a tool in studying brain disease: focus on ultrasonic vocalizations

Organizers: Nicola Simola (Cagliari, IT)

RODENT ULTRASONIC VOCALIZATIONS: BEHAVIOURAL SIGNIFICANCE, MECHANISMS AND USE IN THE STUDY OF DRUG EFFECTS ON THE EMOTIONAL STATE

Nicola Simola, Giulia Costa

Department of Biomedical Sciences, Section of Neuroscience, University of Cagliari, Cagliari, Italy

nicola.simola@unica.it

Aims: Rodents emit ultrasonic vocalizations (USVs) to communicate emotional states. In rats, calls of the 50-kHz USVs group convey positive affect and are increasingly being investigated in studies of reward and motivation. Although the emission of 50-kHz USVs is initiated by the activation of dopamine receptors in the nucleus accumbens shell, additional mechanisms modulate calling of the 50-kHz USVs group. To further elucidate the dopaminergic mechanisms that participate in calling behavior, we investigated the emission of 50-kHz USVs stimulated by the repeated administration of dopaminomimetic drugs in rats bearing a denervation of different dopaminergic regions. Methods: Rats received bilateral injections of 6-hydroxydopamine in either the medial prefrontal cortex (mPFC) or dorsal striatum (DS), or unilateral injections of 6-hydroxydopamine in the medial forebrain bundle (MFB). Thereafter, rats denervated in the mPFC or DS received repeated amphetamine administration, whereas rats denervated in the MFB received repeated apomorphine administration. Results: Rats bearing dopaminergic denervation in the mPFC or DS emitted amphetamine-stimulated 50-kHz USVs, although only rats denervated in the DS emitted 50-kHz USVs when re-exposed to the amphetamine-paired environment. Besides, rats bearing dopaminergic denervation in the MFB emitted apomorphine-stimulated 50-kHz USVs and called at high rates when re-exposed to the apomorphine-paired environment. Conclusions: The present results shed light on how different dopaminergic systems modulate the emission of 50-kHz USVs in rats and may be useful to further clarify the interplay between emission of 50-kHz USVs and drug effects on the emotional state.

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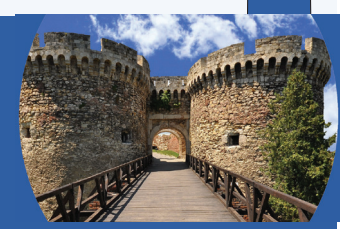

Wednesday, July 11, 2019

8:30–10:10

Room Atlantic 2

Symposium 03

Rodent models of social behavior and emotional states as a tool in studying brain disease: focus on ultrasonic vocalizations

Organizers: Nicola Simola (Cagliari, IT)

USING ULTRASONIC VOCALIZATION IN RATS AS AN INDEX OF AFFECTIVE STATE IN ANIMAL MODELS OF MANIA

Roberto Andreatini

Department of Pharmacology, Federal University of Paraná, Curitiba, Brazil

randreatini@ufpr.br

Bipolar disorder is characterized by episodes of depression and mania, intercalated by euthymia. While we have several animal models of depression that are useful to develop new antidepressant drugs, there are few animal models of mania and they focus in increase locomotor activity mainly. Fifty-kHz ultrasonic vocalizations have been associated with positive affective state in rats and recently we observed that the increase in 50-kHz ultrasonic vocalizations induced by amphetamine was blocked by lithium and tamoxifen, two drugs with clinical antimanic effect. Thus, we proposed that 50-kHz could be a new behavioural readout of manic-like behaviour and we evaluated it usefulness in animal models of mania. Fifty-kHz was increased by sleep deprivation and lisdexamphetamine models of mania, and these increases were blocked by lithium. However, 50-kHz was unchanged in the ketamine model and ouabain administration induced increase both in 50-kHz and 22-kHz USV (this latter subtype has been related to negative affective state). All these animal models of mania exhibited hyperactivity. Thus, USV can differentiate animal models of mania (e.g. ouabain model could represent a model for mixed state) and can be a useful readout in the study of manic-like behaviour and new antimanic drugs.

I have no conflict of interest.

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VASOPRESSINERGIC INFLUENCE OF SOCIAL AND EMOTIONAL BEHAVIOR

Dóra Zelena

Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary;
Centre for Neuroscience, Szentágothai Research Centre, Institute of Physiology, Medical School, University of Pécs, Pécs, Hungary

zelena.dora@koki.mta.hu

Vasorpessin is the central regulator of the hypothalamic-pituitary-adrenocortical axis, the main component of stress adaptation. Therefore, vasopressin is thought to contribute to stress-related disturbances (e.g., anxiety). In order to study affective disorders, behavioral studies are performed on animal models. In adult rats, foot shock-induced ultrasonic vocalisations (USVs) provide a useful model of pathological anxiety with objective and efficient measurement of the affective state. Using a natural vasopressin-deficient Brattleboro rat, we confirmed the role of vasopressin in adult anxiety that can be demonstrated by the reduction of foot shock-induced USVs. Anxiety disorders are also prevalent among children, thus the young population should be also studied. The recording of maternal separation-induced USVs is a promising method for new drug development, as testing pups requires a very low amount of drugs. Results from both genetic and pharmacological studies confirmed the role of vasopressin in the emission of separation-induced USVs through V1a and V1b receptors. These results may be interpreted as a sign of anxiolysis, however, we cannot close out the possibility of disturbed social communication. Nevertheless, vasopressin signaling contributes to anxiety, and monitoring the emission of USVs is useful in the development of new treatment strategies for anxiety.

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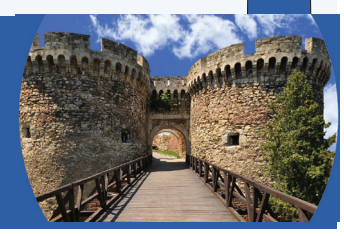

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SOCIAL INTERACTION AND ACOUSTIC COMMUNICATION IN MICE AS MARKERS FOR HEALTHY BRAIN FUNCTION AND BRAIN DISORDERS

Sylvie Granon[1], Frédéric Chauveau[2], Anne Nosjean[1], Alexis Faure[1]

1Paris-Saclay Institute of Neuroscience, Orsay, FRANCE. 2Institut Biomédical des Armées, Brétigny-sur-orge, France

sylvie.granon@u-psud.fr

Adapted social behavior allows both individual and collective well-being. Indeed, virtually all mental health disorders are associated with social deficit. We are interested in understanding the behavioural, neural and neurochemical bases of social cognition and communication using mouse models. We report our recent data showing the crucial role of the prefrontal cortex in the organisation of adapted social interaction, the interplay between the cholinergic and the noradrenergic systems for the balance between affiliative social interaction, dominance and control of aggressiveness, and we will discuss the putative role of ultrasonic communication in social interaction in adult animals. We also report recent data showing the role played by the environment of life and by the context in which interactions take place in healthy individuals. Together, the data presented will offer a novel focus on the social brain –and social life- of rodents and provide some practical recommendations for future experiments.

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Room Mediterranean

SYMPOSIUM 04

HUMAN ELECTROPHYSIOLOGY IN HEALTH AND DISEASE: FROM SINGLE NEURONS TO NETWORKS

Organizers: Andrei Ilie (Newcastle, UK) and Karri Lamsa (Szeged, HU)

ROBUST GABAERGIC SELF-INNERVATION INHIBITS SUPRAGLANDULAR BASKET CELLS IN HUMAN AND MOUSE

Karri Lamsa

University of Szeged, Department of Physiology, Anatomy, Szeged, Hungary

bercziorsi@gmail.com

Autapses are synapse-like self-innervating connections reported in some neurons in the neocortex and certain subcortical brain structures. However, their presence in identified neuron types has been studied very little and their operation in the human neocortex is poorly known. We studied GABAergic inhibitory interneurons in the supragranular layer 2/3 of human neocortical tissue resected in deep brain tumor surgery. Whole-cell recordings revealed $GABA_AR$-mediated self-innervation in most parvalbumin-expressing fast-spiking basket cells (pvBCs). Light- and electronmicroscopic analyses confirmed pvBC axons innervating their own soma and proximal dendrites. Average self-innervation conductance, evoked by unitary action potential, was comparable to strength of synaptic connections made by pvBCs. Autaptic activity heavily overlapped with action potential afterhyperpolarization conductance showing comparable decay time but longer delay and peak times. Computational single-cell simulations demonstrated effective shunting inhibition by GABAergic autapses following a spike. In addition, whole-cell dynamic clamp recordings confirmed effective somatic self-inhibition in pvBCs, whereas most non-fast spiking GABAergic interneurons lacked autaptic inhibition. Autapses were neither found in fast-spiking axo-axonic cells which were prone to fire spike bursts. Finally, we found similar GABAergic self-inhibition in pvBCs in human and mouse indicating that autapses are a general feature in these interneurons in the mammals. Our results here are first to show structural and functional evidence for autaptic self-innervation in the human brain and first to characterize their function in supragranular layer in any mammal. We propose that GABAergic perisomatic self-innervation in supragranular pvBCs has evolved to inhibit irregular or repetitive firing of these interneurons.

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Organizers: Andrei Ilie (Newcastle, UK) and Karri Lamsa (Szeged, HU)

ASSOCIATIVE CIRCUITS IN LAYER 1 OF HUMAN AND MOUSE NEOCORTEX

Rogier B. Poorthuis[1,5], Elisabeth Abs[1], Daniella Apelblat[2], Karzan Muhammad[1], M. Belen Pardi[1], De-Lin Pu[1], Karl-Klaus Conzelmann[3], Huibert D. Mansvelder[4], Ivo Spiegel[2], Johannes J Letzkus[1]

1Max Planck Institute for Brain Research, Frankfurt am Main, Germany;
2Weizmann Institute of Science, Rehovot, Israel;
3Max von Pettenkofer Institute, Munich, Germany;
4Center for Neurogenomics and Cognitive Research, VU University, Amsterdam, Netherlands;
5Present address: Department of Translational Neuroscience, Brain Center University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands

r.b.poorthuis@umcutrecht.nl

Layer 1 is a unique cortical layer comprised of a sparse set of interneurons and distal apical dendrites of pyramidal neurons and thought to integrate information about the behavioral relevance of sensory stimuli processed in the downstream circuit. Top-down information reaches layer 1 through glutamatergic feedback connections and axons originating from neuromodulatory nuclei, which can rapidly recruit layer 1 interneurons to adjust circuit function to current requirements during locomotion, attention and associative learning. It remains little understood whether similar mechanisms exist in the human brain. The function of these cells has also been less studied due to lack of a neuronal marker. We demonstrate that Neuron-derived Neurotrophic Factor (NDNF) is a highly selective marker of layer 1 interneurons in mice and human cortex. In mice, NDNF neurons provide a prolonged form of inhibition onto pyramidal neuron dendrite tufts, strongly affecting dendritic activity. Viral tracing techniques elucidate that these cells receive input from brain regions providing contextual top-down information. During associative learning sensory responses in NDNF neurons become potentiated, showing that this form of inhibition is indeed highly experience dependent. Importantly, these findings extend to the human brain where, next to preserved NDNF expression, human layer 1 also contains two physiologically similar cell types, which are rapidly recruited by nicotinic acetylcholine receptors. These findings imply conserved rapid neuromodulation of human cortical circuits through layer 1. The description of NDNF as a preserved marker for mouse and human layer 1 interneurons will facilitate translation of findings in rodents to the human brain.

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Organizers: Andrei Ilie (Newcastle, UK) and Karri Lamsa (Szeged, HU)

ELECTRICAL FEATURES OF SEIZURE ACTIVITY IN THE BRAIN: BRIDGING THE GAP BETWEEN HUMAN PATIENTS AND ANIMAL MODELS

Andrei Ilie

Institute of Neuroscience, Newcastle University, UK

ilie.andrei.sorin@gmail.com

Aims: Despite the availability of numerous antiepileptic medications around one in three patients with epilepsy continue to suffer from uncontrolled seizure activity, which greatly impairs their quality of life. Hence, there is a need for innovative research aimed at bringing together clinical data from patients and relevant animal models and basic science techniques. Methods and results: I will present our approach to combining basic lab-based research with clinical studies in epilepsy patients with the aim of developing a mechanistic understanding of seizure activity and epilepsy. Conclusion: We hope that such studies will further support the transnational potential of basic science findings and the development of novel rational treatments in epilepsy.

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Organizers: Andrei Ilie (Newcastle, UK) and Karri Lamsa (Szeged, HU)

A BRIEF HISTORY OF INDIRECT WAYS TO ESTIMATE SYNAPTIC POTENTIALS IN HUMAN MOTOR NEURONS

Kemal S. Türker

Koç University School of Medicine, Sariyer, Istanbul

kturker@ku.edu.tr

Since it is not possible to record directly from human neurons, indirect methods have been developed to study their activity. An indirect estimate of synaptic potentials can be obtained by recording the electrical activity in muscles in response to stimulating a set of afferent fibres. Classically, these indirect methods use surface or intramuscular electromyography (EMG) to represent the responses of motor neurons to stimuli. The most common classical techniques are rectification and averaging of EMG around the time of stimulation and compiling peristimulus time histograms from single motor unit records. Limitations of these classical techniques in estimating synaptic potentials have been recognized and reports have claimed that they contain significant errors in estimating underlying potentials (1). We have studied this problem in regularly discharging motoneurons in rat brain slice preparations (2). In these studies, we have illustrated that the classical methods for estimating pathways in central nervous system do in fact contain significant errors and that these errors are minimized when the same discharge rate information is used in a peristimulus frequencygram. This talk aims to highlight the differences between classical and novel methods to illustrate the errors for estimating synaptic potentials / neuronal networks when classical methods are used for estimation.

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SYMPOSIUM 05

PATHOPHYSIOLOGICAL AND CLINICAL APPROACH TO AUTOIMMUNE NEUROPSYCHIATRIC DISEASES

Organizers: Yasemin Gürsoy Özdemir (İstanbul, TR)

IMMUNE CELL INTERACTION AT BLOOD BRAIN BARRIER

Naoto Kawakami[1], Isabel Bauer[1], Nikolaos Kyratsous[1], Ingo Bartholomäus[2], Marija Pesic[1], Hartmut Wekerle[2]

[1]Institute of Clinical Neuroimmunology, University Hospital and Biomedical Center, Ludwig-Maximilians University Munich, Munich, Germany,
[2]Neuroimmunology group, Max-Planck Institute of Neurobiology, Martinsried, Germany

Naoto.kawakami@med.uni-muenchen.de

Multiple Sclerosis (MS) is an autoimmune disease, which is characterized by massive infiltration of immune cells into the central nervous system (CNS). The evidences suggest that encephalitogenic T-cells play critical role for the pathogenesis. To study mechanism of the T-cell infiltration, we used Experimental Autoimmune encephalomyelitis (EAE), an animal model of MS, which is induced by adoptive transfer of encephalitogenic T-cells. It had been shown that the transferred T-cells interact with other types of cells during their migration into the CNS. We explore mechanisms of the interaction around the blood brain barrier (BBB) and consequences of the interaction as critical step to induce CNS inflammation.

To study this, we used intravital two-photon microscopy together with two distinct fluorescent protein based activation sensors. One is fluorescent Resonance Energy Transfer (FRET) based calcium sensing protein, Twitch, which detect the changes of intracellular calcium as early stage of T-cell stimulation. Another is nuclear factor of activated T-cells (NFAT)-GFP fusion protein, which translocate from cytosol to nucleus as later stage of T-cell activation.

Intravital imaging showed that the T-cells appear in blood vessels at spinal cord leptomeninges and migrate on intraluminal surface by integrin alpha4 dependent manner. The T-cells at this stage, they do not show any sign of stimulation. After crossing BBB, T-cells interact with local phagocytes and become activated, detected by long-lasting calcium signaling and NFAT-GFP translocation. The inhibition of any of these interactions ameliorates CNS inflammation and clinical severity. Accordingly, these interactions can be used as target for therapeutic treatments.

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AUTOIMMUNITY IN NEUROBEHÇET DISEASE

Erdem Tüzün

Department of Neuroscience, Aziz Sancar Institute of Experimental and Medical Research, Istanbul University, Istanbul, Turkey

drerdem@yahoo.com

Behçet's disease (BD) is a chronic inflammatory disease of unknown etiology, characterized with recurrent oral aphthae, genital ulcers, skin lesions and uveitis. BD causes a multisystemic vasculitis which affects joints, lungs, gastrointestinal system and central nervous system (i.e. Neurobehçet disease, NBD). Increased proinflammatory and decreased anti-inflammatory cytokines are prominent characteristic features. Both Th1 and Th17-type immunity is enhanced and correlated with the severity of clinical symptoms. Likewise, the cerebrospinal fluid (CSF) of NBD patients exhibits significantly elevated levels of proinflammatory cytokines and B cell-activating factors, some of which are associated with clinical activity, and prognosis. Anti-neuronal antibodies are found in sera and/or CSF of NBD patients, specifically interact with axonal processes and induce neurotoxicity in experimental animals. Moreover, BD patients show increased activity of the innate immunity (e.g. neutrophils, killer cells) leading to an exaggerated response to invading microorganisms. Genetic variants of several cytokines (e.g., IL-10, IL-12, IL-17 and IL-23 receptor), lymphocyte differentiation pathway factors (e.g., STAT3, JAK2) and proteins involved in antigen presentation to T cells (e.g. endoplasmic reticulum aminopeptidase 1 and MHC class I chain-related gene A) have been associated with an increased risk for BD. Functional studies have shown that these genetic variants exert their effects presumably through enhancement of proinflammatory immune responses to pathogens. Although the exact etiopathogenic mechanisms of BD and NBD are still obscure, immunological and genetic studies suggest that they occur as a result of aberrant innate and acquired immune responses triggered by an exaggerated reaction to viral and/or bacterial threats.

LOW PREVALENCE OF AUTOANTIBODIES RELATED TO NEURONAL AND RHEUMATIC AUTOIMMUNE DISEASE IN SERA OF PATIENTS WITH PSYCHOTIC DISORDERS

Carolin Hoffmann[1], Shenghua Zong[1], Marina Mané-Damas[1], Jo Stevens[1], Ashna Silas[1], Gisela Nogales-Gadea[1,2], Maarten J Titulaer[3], Marco W J Schreurs[4], Kishore Malyavantham[5], Vincent C Ramsperger[5], Lakshmanan Suresh[5], Cem İsmail Küçükali[6], Erdem Tüzün[6], Andrei Szoke[7,8,9,10], Marc De Hert[11], Nico J M van Beveren[12], Emiliano González-Vioque[13], Celso Arango[13], Jan GMC Damoiseaux[14], Marc H De Baets[1], Wim A Buurman[1], Peter Molenaar[1], Bart P Rutten[1], Jim van Os[1,15], Mario Losen[1], Pilar Martinez-Martinez[1]

1Department of Psychiatry and Neuropsychology, School of Mental Health and Neuroscience, Maastricht University, Maastricht, the Netherlands. 2Grup de Recerca en Malalties Neuromusculars i Neuropediatriques, Institut d' Investigació Germans Trias i Pujol, Badalona, Spain. 3Erasmus MC University Medical Center, Department of Neurology, Rotterdam, the Netherlands. 4Erasmus MC University Medical Center, Department of Immunology, Rotterdam, the Netherlands. 5IMMCO Diagnostics, Inc. Buffalo, NY, USA. 6Department of Neuroscience, Institute for Experimental Medical Research (DETAE), Istanbul University, Istanbul, Turkey. 7AP-HP, DHU PePSY, Hôpitaux universitaires Henri-Mondor, Pôle de Psychiatrie, Créteil, France. 8INSERM, U955, team 15 « Translational Psychiatry », Créteil, France. 9UPEC, Université Paris-Est, Faculté de médecine, Créteil, France. 10Fondation FondaMental, Créteil, France. 11University Psychiatric Centre Catholic University Leuven, Campus Kortenberg, Kortenberg, Belgium. 12Department of Psychiatry, Erasmus University Medical Center, Rotterdam, the Netherlands. 13Child and Adolescent Psychiatry Department, Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IiSGM, CIBERSAM. Madrid, Spain.14Central Diagnostic Laboratory, Maastricht University Medical Center, Maastricht, the Netherlands. 15Department of Psychiatry, Brain Centre Rudolf Magnus, Utrecht University Medical Centre.

c.hoffmann@maastrichtuniveryity.nl; p.martinez@maastrichtuniversity.nl

Psychiatric symptoms are increasingly recognized as potentially of autoimmune origin, either in the range of newly discovered encephalitis-related antibodies or related to systemic autoimmune diseases like systemic lupus erythematosus (SLE). We aimed to determine the prevalence of neuronal- and systemic autoimmune rheumatic disease (SARD) related-antibodies in sera of patients with psychotic or affective disorder as well as in sera of healthy control subjects. The included cohort comprised 621 individuals diagnosed with psychotic disorders (first episode and chronic), 70 individuals with affective disorders, 41 with other mental disorders, and 257 controls. Overall, 4.1% of all sera showed hippocampal autoantibody binding as detected by reactivity on rat brain tissue using immunohistochemistry (IHC) with no difference between group. Further characterization by live and fixed cell-based assays (CBA) for detecting specific neuronal surface antibodies (NSAbs), and antibodies against glutamic acid decarboxylase (GAD) revealed low prevalence (1.2%) in all groups, and was observed for Caspr2, GAD65 and GAD67 autoantibodies. We identified brain-reactive autoantibodies (in all groups) that target unknown antigens. Two sera (from one individual with schizophrenia and one healthy participant) reacted with live hippocampal neurons. Lastly, SARD-related antibodies, tested by immunofluorescence on HEp-2 substrate were increased in psychotic disorders, but only in 3 patients did antibody testing hint at a possible diagnosis of SLE when analyzing additional enzyme-linked-immuno-assay. Overall, the prevalence of neuronal autoantibodies was very low with no significant difference between healthy controls and patients with mental disorders. Further research into the identification of possible novel antigens and their pathological involvement is warranted.

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PATHOPHYSIOLOGICAL AND CLINICAL APPROACH TO AUTOIMMUNE NEUROPSYCHIATRIC DISEASES

Organizers: Yasemin Gürsoy Özdemir (İstanbul, TR)

AUTOIMMUNE EPILEPSY- FROM SYMPTOMS TO SYNAPSE

Sukhvir Wright

School of Life and Health Sciences, Aston University, Birmingham, UK and Birmingham Children's Hospital, Birmingham, UK

s.wright5@aston.ac.uk

Anti-NMDAR-antibody encephalitis is a well-recognised neuro-immunological syndrome presenting with neuropsychiatric features, seizures and movement disorder. Anti-$GABA_AR$ encephalitis presents with refractory seizures and encephalopathy. The recent development of specific human-derived recombinant monoclonal antibodies from affected patients has allowed exploration of antibody pathogenicity. We have tested the pathogenic effects of these antibodies as well as human IgG in autoimmune epilepsy (AE) animal models using a combination of *in vivo* and *in vitro* techniques. Our results demonstrate that these antibodies are epileptogenic and cause acute and chronic electrophysiological changes in synaptic currents and local field potential recordings *in vitro* as well as in *in vivo* EEG recordings. Characterisation of these epileptogenic effects will allow testing of novel treatments in this potentially treatable epilepsy.

Acknowledgements: SW is supported by an Epilepsy Research UK Fellowship.

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Organizers: Yasemin Gürsoy Özdemir (İstanbul, TR)

AUTOIMMUNITY IN DEMYELINATING NEUROLOGICAL DISEASES

Atay Vural[1,2]

1Koç University School of Medicine, Istanbul, Turkey. 2Koç University Research Center for Translational Medicine

atayvural@gmail.com

Myelin is crucial for proper action potential propagation through axons. Myelin loss, or demyelination, is an important central pathology in several brain disorders and develops secondary to autoimmune mechanisms. Both cell-mediated and antibody-mediated mechanisms can contribute to tissue damage during autoimmunity. Although autoantibodies against myelin proteins have long been looked for in multiple sclerosis (MS), they could be identified in non-MS demyelinating disorders, pointing out to a fundamental difference in their pathogenesis. Antibodies against aquaporin-4 (Aqp4) and myelin oligodendrocyte glycoprotein (MOG) are involved in central demyelinating disorders, and antibodies against paranodal proteins (Neurofascin155, Contactin1 and Caspr) are associated with polyneuropathy. It is intriguing that each of these autoantibodies cause pathology through different mechanisms. While, astrocytopathy is a well-characterized pathogenic mechanism mediated by anti-Aqp4 antibodies, immunopathogenesis of the latter autoantibodies could only be identified recently. Anti-MOG antibodies are of the complement-fixing IgG1 isotype, and they can contribute to demyelination in the presence of tissue infiltrating leukocytes. Anti-neurofascin155 antibodies are of IgG4 isotype, which cannot fix complement, and they do not cause actual myelin loss, but they act through a novel type of pathogenic mechanism named as nodopathy/ paranodopathy. Importantly, presence of these autoantibodies in patients' sera has been associated with specific disease subgroups, even novel diseases, which can be treated with a different therapeutic approach associating the pathophysiological differences with the clinical picture.

In this presentation, I will explain how antibodies targeting different myelin antigens can disturb nerve physiology through different mechanisms, focusing mainly on anti-MOG and anti-neurofascin155 antibodies.

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Room Pacific

SYMPOSIUM 06

STRUCTURAL AND MOLECULAR UNDERPINNINGS OF HUMAN BRAIN DEVELOPMENT

Organizers: Mirjana Maletic-Savatic (Houston, TX, USA)

PROGENITOR CELLS IN THE HUMAN DEVELOPING CEREBRAL CORTEX

Nada Zecevic[1], Nevena Radonjic[1,2], Alberto Ortega[1,3], Fani Memi[1,4]

1Neuroscience Department, University of Connecticut Medical School, Farmington, CT, USA. 2Department of Psychiatry, SUNY Upstate Medical University, Syracuse, NY, USA. 3The Ken & Ruth Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL. 4 Wellcome - MRC Cambridge Stem Cell Institute, Cambridge, UK

nzecevic@uchc.edu

Aims:The mammalian neocortex has evolved during evolution, yet most of our understanding of its development is based on observations made in rodents. We studied primate-specific neural progenitor cells and their contribution to the remarkable evolution of the human cerebral cortex. Neural progenitors are fast proliferating cells that have the potential to differentiate into different cell types. We focused on Nkx2.1 positive ($Nkx2.1^+$) cells, progenitors for parvalbumin (PV^+) interneurons and oligodendrocytes.

Methods: Immunohistochemistry, in situ hybridization, in vitro, electroporation.

Results: $Nkx2.1^+$ cells in human are not restricted to the ventral telencephalon as in mouse, but are also present dorsally, in the fetal cerebral cortex. These primate-specific cortical $Nkx2.1^+$ cells have a potential clinical relevance since their selective elimination during development could alter cortical circuitry and function. We studied whether human cortical Nkx2.1 expression is the result of genetic or environmental factors. Ectopically introduced Nkx2.1gene in the mouse embryonic cortex demonstrated that these cells could initiate but not sustain the generation of cortical interneurons, suggesting that additional factors for cortical interneurogenesis are present in human subventricular zone, but are lacking in mice. We investigated the role of Sonic hedgehog (SHH), a known ventral morphogen, in this process. Unlike in mice, SHH is widely present in human fetal cerebral cortex, secreted from various cells. Treatment of human cortical progenitor cells with Shh *in vitro* induced cell proliferation, and expanded the pool of $Nkx2.1^+$ cells in detriment of calretinin progenitors, thus influencing interneuron subtypes generation.

Conclusions: The remarkable complexity of the human cerebral cortex, and the emergence of higher brain functions, have their origin in the diversity of human-specific cortical progenitors within the subventricular proliferative zone.

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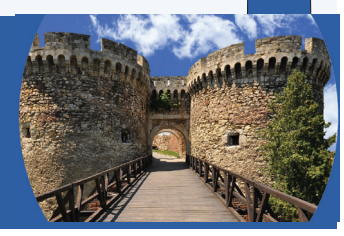

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Room Pacific

SYMPOSIUM 06

STRUCTURAL AND MOLECULAR UNDERPINNINGS OF HUMAN BRAIN DEVELOPMENT

Organizers: Mirjana Maletic-Savatic (Houston, TX, USA)

N-METHYL D-ASPARTATE RECEPTORS (NMDAR) IN HUMAN CORTICAL DEVELOPMENT

Nevena Radonjic[1,2], Inseyah Bagasrawala[1,3], Fani Memi[1,4] Nada Zecevic[1]

1Neuroscience Department, University of Connecticut Medical School, Farmington, CT, USA. 2Department of Psychiatry, SUNY Upstate Medical University, Syracuse, NY, USA. 3Biogen, Cambridge, MA, USA. 4Wellcome - MRC Cambridge Stem Cell Institute, Cambridge, UK

nevence@yahoo.com

Aims: NMDAR are ligand- and voltage-gated ionotropic glutamate receptors that play critical role in synaptic plasticity, development, learning, and memory. To better understand its role in human cortical development we first assessed the NMDAR expression in the fetal cerebral cortex. Further, we used *in vitro* treatment with kynurenic acid (KYNA), an endogenous NMDAR antagonist, to study the effects of transient NMDAR blockade on human cortical progenitor cells. This study is of particular clinical relevance as elevated levels of KYNA have been observed in pregnant women after viral infections and are considered to play a role in neurodevelopmental disorders.

Methods: Immunohistochemistry, in situ hybridization, cell cultures, Western blot, ELISA.

Results: We showed that major NMDAR subunits, NR1, NR2A, and NR2B, are expressed at both mRNA and protein levels, in the human cerebral cortex during the second trimester of gestation. Between 16 and 24 gestational weeks immunohistochemical studies demonstrated that NMDAR subunits are expressed by different cell types within cortical layers. *In vitro* treatment of human cortical progenitors with KYNA decreased their survival and proliferation and resulted in reduced number of neurons. At the same time, the number of activated astrocytes and level of secreted interleukin-6 increased. KYNA treatment reduced differentiation of cortical progenitors into GABAergic neurons, while differentiation into glutamatergic neurons was relatively spared.

Conclusions: The early presence of NMDAR subunits in the human cerebral cortex suggests distinct roles of these receptors in cortical development. Their role in cortical progenitor proliferation and specification was confirmed by *in vitro* blockade via KYNA.

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Room Pacific

SYMPOSIUM 06

STRUCTURAL AND MOLECULAR UNDERPINNINGS OF HUMAN BRAIN DEVELOPMENT

Organizers: Mirjana Maletic-Savatic (Houston, TX, USA)

TRANSGENERATIONAL HEALTH RESEARCH INITIATIVE (THRIVE): ENVIRONMENTAL FACTORS AND *"IN UTERO"* FETAL BRAIN DEVELOPMENT IN URBAN, LOW SOCIOECONOMIC STATUS WOMEN

Erin Miller, Liam Bell, Madeleine Allocco, Eleanor Deng, David Henderson, Snezana Milanovic

Boston Medical Center, Boston University, USA

snezana.milanovic@bmc.org

Background: Mental illnesses affect a large percentage of the US and worldwide population. Despite studies suggesting associations between paternal and maternal environment and fetal neurodevelopment, comprehensive knowledge of factors that predispose to poor mental health is lacking. Biomarkers research on mental health risks and outcomes among low socioeconomic status (SES) populations is limited. Identification of pregnancy related modifiable health risk factors could lead to strategies for early pregnancy preventative interventions, reduce the risk of adverse health outcomes in vulnerable children and thereby ameliorate health care costs.

Aims: Conducting a study in the low SES patient population, typically experiencing complex barriers to care and with consequentially inconsistent adherence to clinical care, is a formidable task. Therefore, our first aim (Aim 1) was to establish interdepartmental research infrastructure ensuring satisfactory subject recruitment and retention as well as strategies aimed at consistent clinical and biological data collection. Our second goal (Aim 2) was to identify a set of newborn biomarkers correlating with high and low environmental stress exposure during pregnancy in the pilot cohort of 100 mother-newborn pairs. Our final, long term goal (Aim 3) is to identify the outcomes of *"in utero"* genome and epigenome interactions on brain development by focusing on downstream metabolic changes indicative of possible behavioral risk or resilience. Here, we present data gathered through execution of the first aim and highlight second aim progress.

Methods: Aim 1 encompasses engagement of the stake holders from five departments and two core centers (Departments of OBGYN, Pediatrics, Radiology, Psychological and Brain Sciences, Mathematics and Statistics, Pathology Lab, Biomedical Imaging Center), identifying collaborators at each site, building up the Team, research infrastructure, protocol and procedures. Aim 2 is up to 9-month pilot study on mothers and fathers, pregnancy and early postpartum, and infants within their first month of life. Data collection includes clinical phenotyping (diet, physical activity, stress, anxiety and depression, medical co-morbidity, fluid intelligence, social support), biobank repository (blood, cord blood and placenta) and neonatal multimodal brain imaging (structural MRI and spectroscopy).

Results: We will highlight data on how the state of mother's stress, anxiety and depression impact perinatal dietary choices and present pilot neonatal neuroimaging data, structural and spectroscopy.

Discussion: THRIVE initiative is a complex interdepartmental research project engaging urban, low SES patients, whereby integrating clinical phenotyping with the biological data collection, in pregnancy and early postpartum. Our pilot study successfully established a viable model for this kind of effort in the low SES inner city population with the long-term goal of identifying biological signatures associated with behavioral risk or resilience status.

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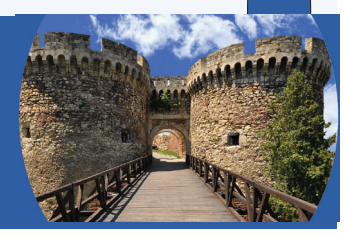

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SYMPOSIUM 06

STRUCTURAL AND MOLECULAR UNDERPINNINGS OF HUMAN BRAIN DEVELOPMENT

Organizers: Mirjana Maletic-Savatic (Houston, TX, USA)

FATTY ACIDS AS BIOMARKERS OF HIPPOCAMPAL ADULT HUMAN NEUROGENESIS

Mirjana Maletic-Savatic

Baylor College of Medicine and Duncan Neurological Research Institute;
Texas Children's Hospital, Houston, Texas, USA

maletics@bcm.edu

The discovery of adult neurogenesis has opened a new era in modern neurobiology: the brain, after all, has the capacity to regenerate. In the mammalian brain, new neurons are continuously formed in two brain regions: hippocampus, the center for learning and memory, and the subventricular zone, from which new neurons migrate to the olfactory bulb. In animal models, newborn neurons are important for cognition, mood and stress regulation. In humans, whether neurogenesis occurs after puberty is still under debate. Regardless, the functional importance of newborn neurons is not known because of the lack of a live and non-invasive measure. Based on a series of experiments using magnetic resonance spectroscopy (MRS), we previously identified a fatty acid-related metabolite that is highly enriched in neural stem cells and visible on the resonance spectrum. Now, using a newly developed automated method of MRS data analysis, we can distinguish neurogenic and non-neurogenic areas in the human brain. Further, we discovered that the neurogenic signal is associated with age and depression. Strikingly, in medication-resistant depressed individuals, electroconvulsive treatment provokes a two-fold signal increase – a leading indicator that predicts subsequent hippocampal plasticity and clinical outcome. Overall, we now have the means to study neurogenesis in the live human brain and provide new insights on the role of this process in human brain function, dysfunction and treatment response.

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SYMPOSIUM 06

STRUCTURAL AND MOLECULAR UNDERPINNINGS OF HUMAN BRAIN DEVELOPMENT

Organizers: Mirjana Maletic-Savatic (Houston, TX, USA)

INNOVATIVE CHEMICAL STRATEGIES FOR MODULATING NEUROGENESIS

Damian W. Young

Center for Drug Discovery, Baylor College of Medicine, Houston, TX, USA

damiany@bcm.edu

One of the overarching aspirations for the neurogenesis field is the development of pharmacological agents that promote the controlled proliferation and differentiation of neural stem cells (NSCs). However, many of the cellular protein targets (i.e. transcription factors) that are emerging that stimulate neurogenesis are considered "undruggable". Hence, new and innovative chemical strategies are needed to modulate the compendium of proteins involved in regulating neurogenesis. To meet this challenge, we are applying Diversity-Oriented Synthesis (DOS) a chemical guiding strategy focusing on the generation of diverse molecular structures to two different screening paradigms: Fragment Based Drug Discovery (FBDD) and DNA-Encoded Chemical Libraries (DECL). Our platforms are well suited to produce ligands to a variety of biological targets, including the more challenging targets required for modulation of neurogenesis.

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SYMPOSIUM 07

IMAGING AND MODELING APPROACHES IN NEUROSCIENCE

Organizers: Dejan Zecevic (New Haven, CT, USA)

DEFINING THE FUNCTIONS OF OLFACTORY BULB PROCESSING VIA COMPARISON OF INPUT AND OUTPUT: ADAPTATION

Douglas A. Storace[1,2], Lawrence B. Cohen[2,3]

1Florida State University, Tallahassee, FL, USA;
2Yale University, New Haven, CT, USA;
3KIST, Seoul, Korea

lawrence.b.cohen@hotmail.com

Humans and other animals exhibit adaptation to odorants. It remains unclear whether the olfactory bulb, the brain structure that mediates the first stage of olfactory information processing, participates in generating this perceptual adaptation. Olfactory bulb glomeruli are regions of neuropil that contain input and output processes; olfactory receptor neuron nerve terminals (input) and mitral/tufted cell apical dendrites (output). Differences between the input and output of a brain region define the function(s) carried out by that region. We compared the activity signals from the input and output to repeated odor stimulation across a range of odorant concentrations. Repeated odor stimulation of the same concentration resulted in a decline in the output maps, while the input remained relatively stable. These results suggest that the mammalian olfactory bulb may participate in the perception of adaptation. Earlier results showed that the bulb participates in generating a concentration invariant odor perception. Thus the olfactory bulb carries out two perceptual computation simultaneously. Our approach may be useful for understanding the role of the olfactory bulb in other olfactory perceptions, and should also be useful for determining the input-output transformation in other regions of the mammalian brain.

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SYMPOSIUM 07

IMAGING AND MODELING APPROACHES IN NEUROSCIENCE

Organizers: Dejan Zecevic (New Haven, CT, USA)

MEMBRANE POTENTIAL FLUCTUATIONS: NOT THAT NOISY

Efstratios K. Kosmidis

Department of Medicine, Aristotle University of Thessaloniki, Greece

kosmidef@med.auth.gr

Field potentials recorded from *in vitro* and *in vivo* brain preparations reveal power law scaling in the distribution of event size phenomena termed "neuronal avalanches" suggesting the approach to a critical state. Based on these observations several authors have promoted the idea that an ensemble of interacting neurons can be simulated by networks operating near a critical point maximising the information processing capacity of the system and linking brain activity across different levels of organisation. Criticality has been linked to excitation at both the single-cell and network levels, as action potential generation marks an obvious phase transition from a resting to an excitable state. Using *in vitro* intracellular recordings, we examine irregular, small amplitude membrane potential fluctuations from CA1 pyramidal neurons of Wistar male rats. We show that these fluctuations, confounded with noise, carry information relevant to the neuronal state. The underlying dynamics exhibit intermittent characteristics shown to describe the temporal fluctuations of the order parameter of a macroscopic system at its critical point even in the absence of firing. The same dynamics emerge from analysing GEVI-expressing (Genetically Encoded Voltage Indicators) cortical neurons in mouse slice preparations. The implications of these findings are discussed.

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SYMPOSIUM 07

IMAGING AND MODELING APPROACHES IN NEUROSCIENCE

Organizers: Dejan Zecevic (New Haven, CT, USA)

ELECTRICAL SIGNALING IN THE AXON: THEORY, PREDICTIONS AND MEASUREMENTS

Popovic, M.A.[1,2], Hanemaaijer, N.A.K.[2,3], Cohen, C.C.[2,3], Klooster, J.[2], Kole, M.H.P.[2,3]

1MCBI, Amsterdam UMC locatie VUmc, Amsterdam, Netherlands;
2Nederlands Herseninstituut, AXS, Amsterdam, Netherlands;
3Utrecht University, Cell Biology, Faculty of Science, Utrecht, Netherlands

m.popovic@vumc.nl

Vertebrate neurons have developed a complex arrangement of voltage-gated ion channels expressed at high densities in domains of myelinated axons to optimize action potential (AP) initiation, conduction and transmitter release. In layer 5 neocortical pyramidal neurons the proximal main axon is myelinated by oligodendrocytes. The myelin sheath accelerates AP propagation causing a rapid saltatory or 'jumping' mode of action potential propagation from one node of Ranvier to the next while keeping the AP signals in the axon initial segment and nodes of Ranvier are extraordinarily fast (~2 kV/s).

To study how ion channels and membranes work in sync to ensure axonal function we implemented and improved high-speed (20 kHz) micrometer precision epifluorescence voltage sensitive dye (VSDI), sodium and calcium imaging methods in combination with electrical recordings, computational modeling, electron microscopy and immuno-labeling.

Using these methods, we discovered that the periaxonal space, the nanoscale submyelin fluid pathway between the axon membrane and myelin sheath is crucial for both saltatory conduction and acceleration of action potentials. Furthermore, high-speed Ca2+ imaging revealed substantial signals in the axon which were spatially confined to the AIS and the nodes of Ranvier during subthreshold depolarizations preceding the AP generation. Subthreshold signals were unaffected by Ca2+ channel blockers, but were effectively abolished by the application of Na+ blockers, leading to the hypothesis that there is a measurable leak of calcium through sodium channels in domains with high Na+ channel density and small volume.

Thesedatashowthatepifluorescenceimagingofaxonalcompartmentsopensupnewresearchavenuesintothestudyofaxonalbiophysics.

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Symposium 07

Imaging and modeling approaches in neuroscience

Organizers: Dejan Zecevic (New Haven, CT, USA)

SYNAPTIC SIGNAL INTEGRATION IN INDIVIDUAL DENDRITIC SPINES

Dejan Zecevic

Yale University School of Medicine, New Haven, CT USA

dejan.zecevic@yale.edu

Electrical properties of neurons are extraordinarily complex and impossible to predict in the absence of detailed measurements. To obtain such a measurement one would, ideally, like to be able to monitor electrical subthreshold events as they travel from synapses on distal dendrites and summate at particular locations to initiate action potentials. It is now possible to carry out these recordings using voltage imaging. We combine voltage imaging and glutamate uncaging using computer-generated holography (CGH). The results demonstrated that patterned illumination reduces photodynamic damage. Additionally, region-specific illumination practically eliminated the contamination of optical signals from individual spines by the scattered light from the parent dendrite. Using this methodology, we showed, in several classes of principal cortical neurons, that synapses on spines are not electrically isolated from the parent dendrites. We next explored the temporal summation of evoked quantal EPSPs at single synapses. At high frequency of synaptic activation (100 to 200 Hz), both the electrical EPSC signal from the soma and the local optical EPSP signal from spines exhibit temporal summation. However, the summating signals saturated at a range of values from 15 - 80 pA for somatically recorded EPSCs and from 3 - 17 mv for optically recorded local EPSPs. This feature prevents synaptic saturation by maintaining the synaptic driving force approximately constant during repetitive activation of synapses. Our preliminary data argue that AMPA-R desensitization is responsible for the saturation of EPSP response in spines during repetitive synaptic stimulation.

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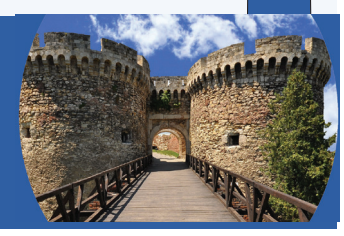

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SYMPOSIUM 07

IMAGING AND MODELING APPROACHES IN NEUROSCIENCE

Organizers: Dejan Zecevic (New Haven, CT, USA)

GLUTAMATE MEDIATED DENDRITIC AND SOMATIC PLATEAU POTENTIALS IN CORTICAL PYRAMIDAL NEURONS

Srdjan D. Antic

University of Connecticut Health, 263 Farmington Ave., Farmington, CT 06030, USA

antic@uchc.edu

Integration of electrical signals in dendrites is essential for brain functions in health and disease. We investigated the voltage waveforms of glutamate-mediated local dendritic plateau potentials using voltage-sensitive dye imaging and somatic electrode recording in rat neocortical brain slice, and via computer simulation. In basal dendrites, dendritic plateaus showed a threshold and increased duration with increased glutamate stimulation. When threshold in dendrite is reached, the spread of voltage from dendrite to cell body causes sustained ~20 mV depolarizations of the cell body. Dendritic plateau potentials occurring in basal dendrites could trigger back-propagating action potentials. Our model replicated these and other experimental observations and makes the following testable predictions: (i) membrane time constant is shortened during the plateau (later confirmed experimentally); (ii) other synaptic responses are more effective during the plateau potential due to both depolarization and time constant change. These results support our hypothesis that dendritic plateaus provide a time window of 200-500 ms during which a neuron is particularly excitable. At the network level, this predicts that sets of cells with simultaneous plateaus would provide an activated ensemble of responsive cells with increased firing. Strong and clustered glutamatergic inputs will have a major influence on activity at both neuronal and network scales. In cortical networks, plateaus across multiple cells would provide an activated ensemble lasting 200-500 ms, within which synchronous spiking could readily occur.

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SYMPOSIUM 08

TEMPORAL LOBE EPILEPSY: FROM CELLS TO MOLECULES

Organizers: Ivan Spasojevic (Belgrade, RS) and Aleksandar Ristic (Belgrade, RS)

HIPPOCAMPAL ANTIOXIDATIVE SYSTEM IN EPILEPSY

Aleksandar J. Ristić,[1] Danijela Savić,[2] Dragoslav Sokić,[1] Jelena Bogdanović Pristov,[3] Jelena Nestorov,[2] Vladimir Baščarević,[4] Savo Raičević,[4] Slobodan Savić,[5] Ivan Spasojević[1]

1Center for Epilepsy and Sleep Disorders, Neurology Clinic, Clinical Center of Serbia, Belgrade, Serbia;
2Institute for Biological Research "Siniša Stanković," University of Belgrade, Belgrade, Serbia;
3Institute for Multidisciplinary Research, University of Belgrade, Belgrade, Serbia;
4Institute for Neurosurgery, Clinical Center of Serbia, Belgrade, Serbia;
5Institute of Forensic Medicine, Medical School, University of Belgrade, Belgrade, Serbia

redoxsci@gmail.com

Mesial temporal lobe epilepsy associated with hippocampal sclerosis (mTLE-HS) is probably the single most frequent human focal epilepsy. The involvement of redox processes in the pathological mechanisms of mTLE-HS has been implicated by mitochondrial dysfunction and oxidative damage, and by different metabolic abnormalities that have been observed in sclerotic hippocampi, such as altered metabolism of redox-active metals. The strongest proof came with the analysis of enzymatic antioxidative system. Sclerotic hippocampi show drastically increased activity and levels of hydrogen peroxide–removing enzymes – catalase and glutathione peroxidase/reductase. Catalase is located mainly in neurons in both, controls and HS. Sclerotic hippocampi are depleted of glutathione peroxidase-positive blood vessels that are present in control hippocampi. Pertinent to this, it has been documented that hippocampi of mTLE-HS patients show increased blood vessel density, but most of the vessels represent atrophic vascular structures. On the other hand, HS showes specific glutathione peroxidase-rich loci that are present in gyrus dentatus, CA regions, and alveus, and appear to represent bundles of astrocytes. These loci are probably sites of excessive (neuronal) production of hydrogen peroxide that is counteracted by astrocytes. Finally, protein levels of mitochondrial enzyme manganese superoxide dismutase are higher in HS than controls. Neurons with abnormal morphology and strong superoxide dismutase immunofluorescence are present in all neuronal layers in HS. In close, antioxidative system is upregulated in HS implying that epileptogenic hippocampi are exposed to oxidative stress. The involvement of redox alterations in the pathology of epilepsy may open new pharmacologic perspectives for mTLE-HS treatment.

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Organizers: Ivan Spasojevic (Belgrade, RS) and Aleksandar Ristic (Belgrade, RS)

MODULATING PROMOTER ACTIVITY TO TREAT INTRACTABLE EPILEPSY

Gabriele Lignani

UCL Queen Square Institute of Neurology, Depart. Clinical and Experimental Epilepsy, London, UK

g.lignani@ucl.ac.uk

Aims: Epilepsy is one of the most important health burdens within the clinical neurosciences, and finding tools that open new mechanistic and therapeutic insights is a high priority. CRISPR is a powerful gene editing approach and it is now starting to be used to cure several pathologies. A variant of CRISPR, CRISPRa, allows to directly regulating the expression of endogenous genes by directly targeting their promoters (PromoTerapy), which allows expression of the full panoply of splice variants and untranslated regulatory sequences.

Methods: In order to determine whether this strategy can be effective in genetic and non-genetic focal epilepsies, we applied CRISPRa technology to increase KNCA1 (encoding for Kv1.1) expression in excitatory pyramidal neurons in a mouse model of focal epilepsy.

Results: The overexpression of Kv1.1 leads to a decreased neuronal excitability, restoring physiological network activity. We have combined the functional analysis of neurons in vitro with the in vivo characterization of its translational potential through telemetry video-EEG.

Conclusions: This approach is considered the proof of principle that PromoTerapy can be used to treat intractable focal epilepsies through the direct regulation of endogenous genes.

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SYMPOSIUM 08

TEMPORAL LOBE EPILEPSY: FROM CELLS TO MOLECULES

Organizers: Ivan Spasojevic (Belgrade, RS) and Aleksandar Ristic (Belgrade, RS)

GABAERGIC MEDIAL SEPTAL NEURONS AND THEIR ROLE IN MODELS OF TEMPORAL LOBE EPILEPSY

Alfredo Gonzalez-Sulser

Centre for Discovery Brain Sciences – University of Edinburgh, UK

agonzal2@ed.ac.uk

Aims: New treatment strategies are needed for temporal lobe epilepsy (TLE) as one third of patients do not achieve seizure control with current medications or surgical procedures. Medial septum GABAergic projection neurons (MSGPNs) specifically target GABAergic cells throughout the hippocampal formation and generate hippocampal theta oscillations (4-12 Hz). MSGPNs exert a powerful influence over network activity in the hippocampal formation, which are brain areas that generate seizures in TLE. Our aim is to determine whether modulation of the activity of MSGPNs could be a viable therapeutic target to treat TLE.

Methods: We have characterised MSGPN projections to the hippocampus in the mouse intrahippocampal and intramygdalaar kainate chronic models of epilepsy. We utilized VGAT::Cre mice in combination with viral injections to express cre-dependant fluorescent proteins GFP, in axons, and mRuby tagged to synaptophysin, in putative synaptic terminals. We also expressed channelrhodopsin-2 in MSGPNs and assessed whether local field potential oscillations in the hippocampus could be entrained before and after epilepsy upon optical stimulation. Finally, we are testing whether wireless optogenetic stimulation modulates seizure duration.

Results: Parvalbumin, calbindin and VGAT positive MSGPN populations are unaffected by chronic epileptic conditions 2 to 3 weeks after kainate injections. We also found intact projections and putative synaptic boutons from MSGPNs to the hippocampal formation. Furthermore, we are able to entrain theta oscillations in the hippocampal formation by optically stimulating MSGPNs expressing channelrhodopsin-2 before and after chronic seizures are established.

Conclusions: Based on these findings, we hypothesise that by optogenetically modulating the activity of MSGPNs we will be able to control oscillations in chronically epileptic animals and change seizure dynamics across the hippocampal formation. We propose MSGPN specific stimulation as a potential novel therapeutic strategy to attain seizure control in patients with TLE.

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SYMPOSIUM 08

TEMPORAL LOBE EPILEPSY: FROM CELLS TO MOLECULES

Organizers: Ivan Spasojevic (Belgrade, RS) and Aleksandar Ristic (Belgrade, RS)

EFFECT OF EXPERIMENTAL TEMPORAL LOBE EPILEPSY ON HIPPOCAMPAL GABAERGIC INHIBITION

Tibor Szilágyi, Rita-Judit Kiss, István Mihály, Károly Orbán-Kis

Department of Physiology, University of Medicine and Pharmacy, Târgu Mureș, Romania

szilagyi67@gmail.com

Epileptic seizures are characterized by pathologic hyperexcitability and synchronization involving abnormally large cell assemblies. Excitability of neural networks is largely controlled by inhibitory interneurons, which provide general inhibition and temporally regulate the activity of principal cells. Distinct inhibitory cell populations contribute differentially to the formation of coordinated cell assemblies which normally provide a temporal framework for a variety of cognitive functions. Under pathologic conditions, however, they could contribute to the formation of abnormally large cell assemblies.

We quantified the changes of the main interneuron populations in the hippocampal CA1 region using the pilocarpine model of temporal lobe epilepsy in Wistar rats. We studied the density of basket cells that provide perisomatic inhibition, axo-axonic cells that control the output of principal cells, bistratified cells that essentially modulate Schaffer collateral input, oriens-lacunosum moleculare (O-LM) cells that modulate entorhinal cortical input and ivy cells that provide an overall control of excitation. The animals were video-monitored in order to establish seizure pattern and behavior. Part of the animals was sacrificed two days after induction. In this group the density of all detected interneuron subtypes was drastically lower. Another group was sacrificed after the occurrence of spontaneous seizures. The density of perisomatic inhibitory cells and bistratified cells was maintained whereas the density of O-LM and ivy cells was reduced. In the later stage of epileptogenesis the observed density of all interneurons was higher than in the early period, therefore we assume that the early drop is not indicating cellular death, but rather weakening of immunodetectability.

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Symposium 08

Temporal lobe epilepsy: from cells to molecules

Organizers: Ivan Spasojevic (Belgrade, RS) and Aleksandar Ristic (Belgrade, RS)

THE IMPORTANCE OF COPPER IN PATHOLOGY OF MESIAL TEMPORAL LOBE EPILEPSY

Danijela Savić[1], Miloš Opačić[2], Jelena Nestorov[3], Aleksandar J. Ristić[4], Dragoslav Sokić[4], Vladimir Baščarević[5], Savo Raičević[5], Slobodan Savić[6], Maja Zorović[7], Marko Živin[7], Vid Simon Šelih[8], Snežana Spasić[9], Ivan Spasojević[2]

1 Department of Neurobiology, Institute for Biological Research "Siniša Stanković," University of Belgrade, Belgrade; Serbia. 2 Life Sciences Department, Institute for Multidisciplinary Research, University of Belgrade, Belgrade; Serbia. 3 Department of Biochemistry, Institute for Biological Research "Siniša Stanković," University of Belgrade, Belgrade; Serbia . 4 Centre for Epilepsy and Sleep Disorders, Neurology Clinic, Clinical Centre of Serbia, Belgrade; Serbia . 5 Institute for Neurosurgery, Clinical Centre of Serbia, Belgrade; Serbia. 6 Institute of Forensic Medicine, Medical School, University of Belgrade, Belgrade; Serbia. 7 Brain Research Laboratory, Institute of Pathophysiology, Medical Faculty, University of Ljubljana, Ljubljana; Slovenia. 8 Department of Analytical Chemistry, National Institute of Chemistry Slovenia, Ljubljana; Slovenia. 9 Department of Chemistry, Institute of Chemistry, Technology and Metallurgy, University of Belgrade, Belgrade; Serbia

danisto@ibiss.bg.ac.rs

More and more studies are identifying the regulation of metal homeostasis as one of the key points of central nervous system's well-being. Epilepsy is a particularly interesting neurological condition when viewed in terms of the correlation between the amount of metals and the development of a seizure. This lecture will present contribution of our group to the field of metal biology in epilepsy by mapping brain metals in sclerotic hippocampus resected from drug resistant mesial temporal lobe epilepsy (mTLE) patients as surgical therapeutic approach. Direct insight into this epileptogenic area, by two powerful techniques, optical emission and mass spectrometry, has led us to investigation of copper turnover. Namely, among the examined metals, we found the deficiency of copper in sclerotic hippocampus on two levels: (i) in whole structure (ii) and locally in the areas of neuronal loss, with significant correlation between copper concentration and neuron density. Furthermore, analysis of copper metalloproteins showed: (i) significant increase or decrease in levels of protein that is participating in copper transport into the cell (CTR1) depending on the degree of hippocampal neuronal loss; (ii) and lower activity of an enzyme in which copper is part of the active site, cytochrome c oxidase, in sclerotic hippocampi of patients compared to control tissue. In our further investigations it remained to be determined whether changes in copper concentrations and copper metalloproteins are causal to pathology of mTLE or they represent epiphenomenon.

Acknowledgements - this study was funded by the Ministry of Education, Science and Technological Development of the Republic of Serbia, grant numbers III41014 and OI173014, and by Slovenian Research Agency (ARRS), Project numbers P3-0171 and P1-0034.

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Room Mediterranean

Symposium 09

Investigating neural circuit computations and connectivity underlying cognitive function

Organizers: Emre Yaksi (Trondheim, Norway) and Ewelina Knapska (Warsaw, PO)

SOCIALLY TRANSFERRED FEAR IS MODULATED BY OXYTOCIN SIGNALING IN THE CENTRAL AMYGDALA

Ewelina Knapska

The Nencki Institute, Warsaw, Poland

e.knapska@nencki.gov.pl

Sharing emotional states between individuals (emotional contagion) affects attention, learning and memory. The neuronal circuits necessary for sharing emotions are not well understood. We have developed a rat model of socially transferred fear to study emotional contagion and underlying brain mechanisms. We showed that social interaction with a partner that had been recently fear conditioned promotes defensive behavior to potentially dangerous situations in the environment. Socially transferred fear enhances exploratory/risk assessment behaviors, as well as subsequent learning and memory. We found that the behavioral changes are mediated by the neuronal circuit in the central nucleus of the amygdala (CeA). Using c-fos-driven targeting of channel rhodopsin we activated neurons involved in the social interaction with a fearful partner. We showed that activation of these neurons enhances exploratory/risk assessment behaviors. Further, we observed that the socially transfer fear involves CRF-positive neurons and is bi-directionally modulated by oxytocin. Injection of oxytocin receptor antagonist into the CeA enhanced socially transferred fear, whereas increasing oxytocin level reduced the responses of rats that underwent a social interaction with a fear conditioned partner. Collectively, these data suggest that a brief social interaction with a cage mate that has undergone an aversive learning experience facilitates adaptation to the environment, which is mediated by the neuronal circuit in the CeA modulated by oxytocin.

The project was supported by European Research Council Starting Grant (H 415148)

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COGNITIVE ONTOGENY IN HEALTH AND MENTAL ILLNESS: A STORY OF RIGHT COMMUNICATION

Ileana L. Hanganu-Opatz

Developmental Neurophysiology, University Medical Center Hamburg-Eppendorf, Germany

hangop@zmnh.uni-hamburg.de

Cognitive performance relies on the entrainment of neuronal networks in oscillatory patterns of electrical activity. They ensure the spatiotemporal orchestration of neuronal activity and enable information transfer and storage, as exemplified in the case of functional interplay between the prefrontal cortex and hippocampus. Coupling of the neuronal networks in oscillatory rhythms is not a hallmark of the adult brain but rather emerges early during development. However, the contribution of coordinated activity for the maturation of neuronal networks accounting for cognitive processing remains largely unknown. The talk will introduce the mechanisms controlling the development of structural and functional coupling within prefrontal-hippocampal networks of rodents from birth until juvenile stage of development. In particular, the cellular interactions accounting for emergence of long-range communication in the immature brain will be highlighted. Moreover, the impaired maturation of functional communication within hippocampal-prefrontal networks, switching from hypo- to hyper-coupling, will be characterized as a possible mechanism underlying the pathophysiology of cognitive deficits in neuropsychiatric disorders.

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Organizers: Emre Yaksi (Trondheim, Norway) and Ewelina Knapska (Warsaw, PO)

THE ROLE OF BASAL FOREBRAIN CELL TYPES IN ASSOCIATIVE LEARNING

Balazs Hangya

Institute of Experimental Medicine, Budapest, Hungary

hangya.balazs@koki.mta.hu

Basal forebrain cholinergic neurons (BFCNs) has been implicated in learning, memory, attention, arousal, plasticity and other aspects of cognition. Besides BFCNs, the basal forebrain also contains GABAergic and glutmatatergic projection neurons. Parvalbumin (PV)-expressing GABAergic neurons has been shown to be crucial for oscillatory coupling between basal forebrain, hippocampus and neocortex, important for learning and attention. Both a mechanistic understanding of the role of the cholinergic system in cognition as well as how other basal forebrain cell types participate in this circuit are missing. To address this, we recorded the activity of optogenetically identified BFCNs and PV-expressing GABAergic neurons in mice performing associative learning tasks. We found that BFCNs showed an activity pattern most likely reflecting a strong role in reinforcement learning, while GABAergic neurons were more heterogeneous across subregions of the basal forebrain, likely supporting roles in attention and aversion. Oscillatory coupling between the medial septum of the basal forebrain and the hippocampus mostly relied on the interaction of different subtypes of GABAergic neurons within the medial septal circuit.

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Symposium 09

Investigating neural circuit computations and connectivity underlying cognitive function

Organizers: Emre Yaksi (Trondheim, Norway) and Ewelina Knapska (Warsaw, PO)

STUDYING THE FUNCTION OF ONGOING ACTIVITY AND FUNCTIONAL CONNECTIVITY OF HABENULAR NETWORKS

Emre Yaksi

Kavli Institute for Systems Neuroscience, NTNU, Trondheim, Norway

emre.yaksi@ntnu.no

The habenula (Hb) is a brain region with increasing popularity due to its strong link to addiction, mood disorders and associative fear learning. We demonstrated that Hb neurons respond to odors and light asymmetrically. Moreover, we showed that Hb neurons exhibit structured ongoing activity that is spatially and temporally organized. This ongoing activity resembles neural attractors, which can switch the preferred state of the Hb and regulate the transmission of sensory information to downstream monoaminergic brainstem nuclei. In order to explore the source of Hb spontaneous activity, we investigated the local connectivity within Hb and the global functional inputs to Hb. Our results showed that recurrent excitatory connections within Hb is important for maintaining spatio-temporal organization of Hb activity. Moreover, we observed that functional inputs form zebrafish homologue of amygdala and sensory inputs from visual and olfactory systems are the major drivers of ongoing Hb activity. Our results suggested that limbic and sensory inputs are integrated in Hb in a non-linear fashion. We also showed that sensory inputs to Hb disengages the communication between amygdala and Hb, thereby regulating the communication between amygdalar circuits and the monoaminergic brain nuclei. We are currently investigating the alterations of ongoing activity and functional connectivity of these circuits during learning and at different emotional states, such as anxiety and fear. We propose that Hb lies in the heart of a brain wide network and act as “a hub” or “a switchboard”, which can regulate or gate the communication of sensory systems and limbic forebrain areas with the monoaminergic brainstem nuclei that control animal behaviors.

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SYMPOSIUM 10

THE OREXIN/HYPOCRETIN SYSTEM ORCHESTRATES MULTIFACETED PHYSIOLOGICAL FUNCTIONS

Organizers: Chiara Berteotti (Bologna, IT)

SLEEP AND CARDIOVASCULAR STUDIES IN NARCOLEPTIC MICE

Chiara Berteotti

PRISM Laboratory, Dept. Biomedical and NeuroMotor Sciences, University of Bologna, Italy

chiara.berteotti@unibo.it

The hypothalamic neurons releasing the orexin (hypocretin) peptides widely project to all brain regions, and specifically reach arousal-promoting neurons; the loss of orexin neurons is associated with narcolepsy. Narcolepsy is a chronic and rare neurodegenerative disease that entails excessive daytime sleepiness, often linked to sudden episodes of muscle weakness (cataplexy). A remarkable feature of narcolepsy is its wide comorbidity spectrum, which includes metabolic, cardiovascular, and respiratory anomalies. Narcoleptic, orexin- deficient mice represent a powerful model for the interpretation of physiological dysregulation due to an impairment of orexin signalling. It is still unclear whether the different narcolepsy traits depend on the direct loss of orexin neurons or on the loss of orexinergic projections to neural structures involved in sleep, metabolic, and cardiorespiratory control, or rather they are indirectly induced by secondary and possibly compensatory imbalances of other transmitter systems. In particular, the hypothalamic wake-promoting histamine neurons are activated by orexin neurons, and could mediate orexins arousal-producing effects. Notwithstanding this strong functional link, brain histamine levels assessment in narcoleptic patients and orexin-deficient mice have yielded inconclusive results, showing either reduced or normal values compared to control subjects. Independent studies recently reported an increased number of histamine neurons in narcoleptic patients but provided contrasting results on orexin-deficient mice. These results, together with those obtained in double-mutant mice, with an impairment of both orexin and histamine system, indicate that imbalances of histamine transmission have the potential to impact significantly on narcolepsy pathophysiology, at least as far as the sleep phenotype is concerned.

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THE OREXIN/HYPOCRETIN SYSTEM ORCHESTRATES MULTIFACETED PHYSIOLOGICAL FUNCTIONS

Organizers: Chiara Berteotti (Bologna, IT)

THE PSYCHOLOGICAL AND PSYCHOSOCIAL PROFILE OF NARCOLEPSY TYPE 1: YOUNG AND ADULT PATIENTS.

Christian Franceschini[1], Maria Claudia Folli[1], Giuseppe Plazzi[2]

1Department of Medicine and Surgery, University of Parma, Italy;
2Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy

christian.franceschini@unipr.it

Narcolepsy is a disabling, rare, and chronic sleep disorder, that arises in childhood or adolescence and is characterized by excessive daytime sleepiness (EDS), cataplexy and others REM-sleep dysregulation (i.e. hallucinations, sleep paralysis). Two distinct subtypes of narcolepsy have been defined by ICSD –III (2014): narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2), both of which have similar clinical profiles, except for the incidence of cataplexy, which occurs only in patients with NT1. The loss of hypocretin (also called orexin) in dorsolateral hypothalamus neurons may lead to NT1. The cause behind this fact has still not been fully cleared yet, but it is thought to be an autoimmune process possibly triggered by both genetic and environmental risk factors; hypothesis based on the strong association with human leukocyte antigen (HLA) DQB1*0602 and other genetic features.

In pediatric cases, NT1 is characterized by a dramatic level of severity accompanied by behavioral, metabolic, endocrinological, neuropsychiatric features, cognitive impairment, and mood disorders. This clinical picture gradually develops into the most typical adult form. This may in part clarify why it has been so difficult to recognize the exact diagnosis (±15 years after the onset of symptoms). Current data suggest that narcolepsy, both in adults and childhood cases, have a global impact on functioning, quality of life, employment, and efficiency. These factors are expected to contribute to a substantial economic, productivity and health-care burden on narcolepsy patients.

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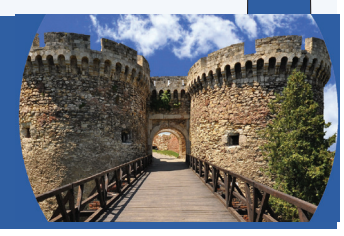

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THE OREXIN/HYPOCRETIN SYSTEM ORCHESTRATES MULTIFACETED PHYSIOLOGICAL FUNCTIONS

Organizers: Chiara Berteotti (Bologna, IT)

STUDY OF MELANIN CONCENTRATING HORMONE AND OREXIN/HYPOCRETIN NEURONS IN THE PRADER-WILLI SYNDROME

Pace M[1], Falappa M[1,2], Freschi A.[1], Tucci V[1]

1Department of Neuroscience and Brain Technologies, Istituto Italiano di Tecnologia, Genova, Italy;
2Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DINOGMI), Università degli Studi di Genova, Genova, Italy

marta.pace@iit.it

Introduction: Prader-Willi syndrome (PWS) is a paternally imprinted disorder that leads to sleep, feeding alterations and temperature instability. All these functions are regulated by the hypothalamic area. We hypothesized that two neuronal populations located in the lateral hypothalamus (LH), the melanin-concentrating hormone (MCH) and on the orexin/hypocretin (OX) neurons that play a major role in controlling most the behavioral alterations observed in the PWS are compromised.

Methods: Mice with paternally inherited Snord116 deletions, that is one of the best candidates for PWS, (PWS-mice) and wild-type littermate control (WT-mice), were used. We assessed in these mice the neuronal firing of the LH by single unit activity (SUA) across the sleep-wake cycle recorded by EEG/EMG electrodes. Thus, molecular biological characterization of the MCH and OX systems were performed.

Results: Our data show that the neuronal firing of the LH had a different neuronal distribution between the two genotypes of mice. These discrepancies between the proportion of neuronal activity among groups may be explained by a significant reduction of OX-expressing neurons in the LH with a concomitant reduction of the OX-protein levels in the PWS mice. Conversely, MCH-expressing neurons were unchanged between the two genotypes of mice.

Conclusion: Our data, for the first time, describe that the orexin system is altered in mice with a paternal deletion of the Snord116 gene. The unbalance between the OX and MCH neurons may explain the sleepiness observed in these mice and in PWS subjects. Finally, this study provides new evidence for the therapeutic approach for PWS.

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Organizers: Chiara Berteotti (Bologna, IT)

OREXIN AND ALZHEIMER'S DISEASE

Claudio Liguori

Sleep and Epilepsy Centre, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

dott.claudioliguori@yahoo.it

In the recent years, orexinergic system dysregulation has been described in Alzheimer's Disease (AD) neurodegenerative process. In human studies, it has been demonstrated that both patients affected by moderate-severe AD and patients affected by mild cognitive impairment (MCI) due to AD pathology show increased CSF orexin levels compared to controls. These findings suggested that the orexinergic neurotransmitting system may be dysregulated in the early as well as in the advanced stages of the AD neurodegenerative processes.

It is well known that the role of the orexinergic system is not limited to the control of diurnal wake, but also influences nocturnal sleep. In physiologic condition, higher orexin cerebral levels seems to reduce primarily REM and slow wave sleep and increase wakefulness during nocturnal sleep; whereas during the day the higher orexinergic tone promotes daytime wakefulness. The finding that CSF orexin levels are higher in AD and MCI patients and correlate with sleep dysregulation proposed that orexinergic signaling dysregulation coupled with nocturnal sleep alteration can be responsible for circadian rhythm disruption in AD patients. Animal model studies supported this finding by demonstrating that modulation of orexin and its effects on sleep appear to induce β-amyloid pathology in the brain.

Taking into account that Alzheimer's pathology interferes with sleep physiology, orexinergic system dysregulation may play a significant role in altering sleep in AD patients and promoting AD pathology by inducing β-amyloid neurodegeneration. Hence, we will show the recent evidence about the relationship among orexinergic signaling overexpression, the disruption of the sleep-wake cycle and AD pathology.

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SYMPOSIUM 11

FROM GENES TO MEMORY: WHAT BRAIN PATHOLOGY TELLS US ABOUT ITS NORMAL FUNCTION

Organizers: Natalia N. Nalivaeva (Leeds, UK) and Illana Gozes (Tel Aviv, IL)

ADNP AS A MASTER REGULATOR OF COGNITIVE FUNCTIONS IN AUTISM AND BEYOND

Illana Gozes

Lily and Avraham Gildor Chair for the Investigation of Growth Factors, Elton Laboratory for Molecular Neuroendocrinology, Department of Human Molecular Genetics and Biochemistry, Sackler Faculty of Medicine, Sagol School of Neuroscience and Adams Super Center for Brain Studies, Tel Aviv University, Tel Aviv, Israel.

igozes@tauex.tau.ac.il

Activity-dependent neuroprotective protein (ADNP), a protein discovered in our laboratory almost two decades ago, is essential for brain formation and functions. Our most recent discoveries show that ADNP is not only essential for the closure of the neural tube in the developing embryo, but is required for dendritic spine formation at the pre- and post-synaptic densities, and regulates the glutamatergic synapses. This tight regulation is also observed at the gene expression level and translated into control of vocalization, motor functions, as well as object and social memory. These ADNP deficiencies, in a mouse model of haplo- insufficiency are corrected by chronic daily administration of the ADNP snippet, drug candidate NAP (CP201). Mechanistically, NAP enhances ADNP association with microtubule end binding proteins (EBs), essential for dendritic spine formation. EB proteins interact with Tau, a protein important for microtubule dynamics and NAP/ADNP enhance Tau association with the microtubules, with preference to the developmentally associated 3R Tau (three microtubule repeat binding Tau, contrasting with aging associated 4R Tau), suggesting applicability to neurodevelopmental disorders. In this respect, CP201 is currently being developed for the ADNP syndrome, a rare autism spectrum genetic disorder caused by de novo ADNP mutations.

Conflict: Professor Gozes is the Chief Scientific Officer of Coronis Neurosciences developing CP201 for the ADNP syndrome

Publications:

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FROM GENES TO MEMORY: WHAT BRAIN PATHOLOGY TELLS US ABOUT ITS NORMAL FUNCTION

Organizers: Natalia N. Nalivaeva (Leeds, UK) and Illana Gozes (Tel Aviv, IL)

HOW TRAUMATIC BRAIN INJURY IMPAIRS THE MEMORY?

Denes V. Agoston

Department of Anatomy, Physiology and Genetics, School of Medicine, USU B2036; Labs: 2033&2035, Bethesda, MD, USA

denes.agoston@usuhs.edu

Traumatic brain injury (TBI) is the most heterogeneous and complex human condition affecting the most complex organ in the body. One of the frequent consequences of TBI is memory impairment. Depending on the type and severity of the injury, memory impairment can be transient or permanent. The neuroanatomical substrates of memory circuit, primarily the hippocampus (specifically, the dorsal hippocampus) are especially vulnerable to noxious events like TBI. The pathobiological changes after TBI involve wide ranges of pathologies from metabolic changes to inflammation and each one of them can adversely affect hippocampal functions. This presentation will a) discuss the various pathological processes triggered by TBI; b) how these processes affect the cytological and molecular architecture of the hippocampus; c) their functional consequences; and finaly c) it will discuss current and future treatments that can mitigate memory impairment after TBI.

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SYMPOSIUM 11

FROM GENES TO MEMORY: WHAT BRAIN PATHOLOGY TELLS US ABOUT ITS NORMAL FUNCTION

Organizers: Natalia N. Nalivaeva (Leeds, UK) and Illana Gozes (Tel Aviv, IL)

GENE-DEPENDENT MECHANISMS OF HYPOXIC PRECONDITIONING: A CROSS-TALK WITH NEUROPLASTICITY AND MEMORY

Rybnikova E.A., Samoilov M.O., Zenko M.Yu.

Pavlov Institute of Physiology, Russian Academy of Sciences, St.Petersburg, Russian Federation

rybnikova1@rambler.ru

It has been experimentally proven that hypoxic preconditioning (PC) is one of the safest and most effective neuroprotective techniques with high translational potential. For this reason, studying the mechanisms enabled by PC represents a very topical trend regarding both its fundamental and practically-oriented aspects. The results of such studies will promote PC introduction into medical practice, as well as the potential to discover novel targets for drug design. We recently have developed a PC protocol using three sequential episodes of mild hypobaric hypoxia (360 mm Hg, equivalent to 5000 m above sea level) produced in a barochamber. Comparative analysis with other known pro-adaptive techniques, such as high-altitude acclimatization, stress PC, and remote ischemic PC, demonstrated the highest efficacy of our PC technique in rats. In addition, the PC considerably improved working memory and other parameters of cognitive status in old monkeys displaying senile cognitive deficits. Intensive studies of the underlying molecular mechanisms showed that the PC action is closely associated with histone acetylation, activation of transcription factors CREB, c-Fos, NGFI-A and HIF-1, and up-regulation of BDNF and erythropoietin expression in the forebrain neurons of the hippocampus and neocortex. These findings indicate that the mechanisms engaged by the hypoxic PC considerably overlap with the molecular mechanisms of neuroplasticity. It is therefore hypothesized that the phenomenon of PC might be considered as a type of learning rather than of training although this question needs further studies.

The work has been supported by the Presidium of Russian Academy of Sciences (program 1.42.).

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FROM GENES TO MEMORY: WHAT BRAIN PATHOLOGY TELLS US ABOUT ITS NORMAL FUNCTION

Organizers: Natalia N. Nalivaeva (Leeds, UK) and Illana Gozes (Tel Aviv, IL)

ROLE OF EPIGENETIC REGULATION OF AMYLOID-CLEARING PROTEINS IN MEMORY AND NEURODEGENERATION

Natalia N Nalivaeva[1,2], Anthony J Turner[1], Igor A Zhuravin[2]

1School of Biomedical Sciences, Faculty of Biological Sciences, School of Biomedical Sciences, Faculty of Biological Sciences, University of Leeds, Leeds LS2 9JT, United Kingdom;
2Institute of Evolutionary Physiology and Biochemistry 44 Thorez av., 194223, Saint Petersburg, Russia.

n.n.nalivaeva@leeds.ac.uk

Gestational factors play a crucial role in epigenetic regulation of brain development and functions in postnatal life and underlie increased vulnerability of individuals to neurodegeneration, including Alzheimer's disease (AD). The pathogenesis of the sporadic form of AD is connected with impaired amyloid-beta peptide (Abeta) clearance from the brain. In the healthy brain a group of amyloid-degrading enzymes (ADEs) and transport proteins maintain physiologically balanced levels of Abeta, however their expression and activity changes with age or under pathology. The neuropeptidase, neprilysin (NEP), is the major ADE and a therapeutic target in AD. NEP expression and activity in rat cortex and hippocampus decrease with age and they are reduced after prenatal hypoxia (PH) which correlates with impaired memory of the animals. Translating the results of our cell culture studies of the epigenetic mechanisms of regulation of ADEs into an animal model of prenatal hypoxia it was demonstrated that treatment of rats with a histone-deacetylase inhibitor valproic acid or a caspase inhibitor Ac-DEVD-CHO was able to restore decreased levels of NEP expression via the Amyloid Precursor Protein Intracellular Domain (AICD)-dependent mechanism and resulted in improved animal memory. Epigallocatechin gallate treatment of cells and animals also resulted in increased NEP expression and activity and improved memory of animals subjected to prenatal hypoxia. Further studies of ADE regulation will help to design possible strategies for preventing neurodegeneration and memory deficits caused by various pre- and postnatal insults leading to Aβ accumulation.

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Symposium 12

Neuromodulation of brain states in health and disease: bridging experiments and computational models

Organizers: Srikanth Ramaswamy (Lausanne, CH)

ACETYLCHOLINE-DEPENDENT MODULATION OF NEOCORTICAL CIRCUITS.

Joanna Urban-Ciecko[1,2], Jean-Sebastien Jouhanneau[3,4], Stephanie E. Myal[1], James F.A. Poulet[3,4], and Alison L. Barth[1]

1Department of Biological Sciences and Center for the Neural Basis of Cognition, Carnegie Mellon University, Pittsburgh, PA, USA; 2Nencki Institute of Experimental Biology, Warsaw, Poland; 3Department of Neuroscience, Max Delbrück Center for Molecular Medicine (MDC), Berlin-Buch, Berlin, Germany. 4Cluster of Excellence NeuroCure, Neuroscience Research Center, Charité Universitätsmedizin Berlin, Berlin, Germany

j.ciecko@nencki.gov.pl

Acetylcholine is a powerful modulator implicated in cognitive functions and behaviors, including motivation, attention, learning and memory. Understanding how acetylcholine modulates circuit function will require an understanding of how this neuromodulator influences specific neuronal classes and the synapses that link them together.

Aim: Here we focused on a common synaptic motif in neocortical circuits, the excitatory synapse from pyramidal neurons to somatostatin-expressing (SST) interneurons. It has been proposed that this motif is critical to trigger inhibition through SST neurons to prevent recurrent or runaway activity in the circuit.

Methods: We employed a combination of pharmacological screening, optogenetic activation of specific modulatory pathways, and paired whole-cell recordings from layer 2/3 pyramidal to SST pairs in brain slices and in vivo in the somatosensory cortex of mice to examine how synaptic inputs can be altered by cholinergic pathway.

Results: Brief, optogenetically-gated endogenous acetylcholine release in the neocortex significantly enhanced pyramidal to SST synapses but not pyramidal connections to other target neurons in the L2/3 network. These effects were mediated by presynaptic nicotinic receptors and require a delay between acetylcholine release and the enhancement of the release probability. The delayed effect was due to the activation of PKA-dependent signaling in the presynaptic cell.

Conclusions: Brain state and synapse-specific unmasking of ubiquitous connection motifs may be a powerful way to functionally rewire cortical circuit dependent on behavioral demands.

This work was supported by the McKnight Foundation (ALB) and NIH R01NS088958 (ALB and JFAP), the National Science Centre, Poland (2015/18/E/NZ4/00721; JUC), the European Research council (ERC-2015-CoG-682422; JFAP), the DFG (DFG-FOR-2143-Interneuron; JFAP), the Berlin Institute of Health (BIH; JFAP) and the European Union (FP7, 3x3Dimaging 323945; JFAP).

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Symposium 12

Neuromodulation of brain states in health and disease: bridging experiments and computational models

Organizers: Srikanth Ramaswamy (Lausanne, CH)

MIDBRAIN CONTROL OF CONDITIONED LEARNING VIA STRIATAL CHOLINERGIC INTERNEURONS

Giorgio Rizzi, Zhuoliang Li, Norbert Krebs, Kelly R. Tan

Biozentrum, University of Basel, Basel, Switzerland

kelly.tan@unibas.ch

The ability to incorporate information from the environment and use it to update behavior strategies and patterns is the basic principle of reinforced learning. This experience dependent form of learning is perhaps one of the simplest tasks mammals can perform, yet the neurobiological substrate enabling this process is rather complex and not fully understood.

Striatal activity has for decades been implicated in reinforced learning and particularly, cholinergic interneurons have been highlighted as key players in the incorporation and processing of salient predictive stimuli.

At a mechanistic level, these neurons known to be tonically active, respond to relevant cues with a brief pause in their firing. Substantial work dissecting the local connectivity between striatal medium spiny neurons and various interneurons has substantiated the hypothesis that the cholinergic pause opens a timely window that allows for dopaminergic modulation of the striatal circuitry to take place, hence generating the reinforcing signal.

Although considerable work has focused on the effect of this mechanism, much less is known about the upstream circuitry that leads to such a particular neuronal response.

Here we highlight how the midbrain (including the ventral tegmental area (VTA) and substantia nigra (SN)) known to participate in reinforcement, can use different neurotransmitters to drive cholinergic activity in the dorsal striatum. This process occurs both mono-synaptically and via an intermediary thalamic relay, the para-fascicular subdivision (PF).

Furthermore, pathway specific inhibition of these circuits produces differential impairments in a classic fear conditioning task suggesting that each component of such a complex network carries information pertinent to sub domains of the behavioral strategy.

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Wednesday, July 11, 2019

16:10–17:50

Room Atlantic 1

Symposium 12

Neuromodulation of brain states in health and disease: bridging experiments and computational models

Organizers: Srikanth Ramaswamy (Lausanne, CH)

MOTIVATIONAL BIASES IN DECISION-MAKING: PHARMACOLOGY, PSYCHOPATHOLOGY AND COMPUTATIONS

Vanessa Scholz[1], Roxanne Hook[2], Stephanie Valle[3], Elizabeth Cavic[3], Jon Grant[3], Samuel Chamberlain[2], Hanneke den Ouden[1]

1Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands. 2Department of Psychiatry, University of Cambridge, UK and Peterborough NHS Foundation Trust, UK. 3Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, USA

v.scholz@donders.ru.nl

Our motivations strongly shape our behaviour, even in a seemingly automatic fashion. While rewards usually elicit behavioural activation, a threat of punishment tends to evoke behavioural inhibition. These motivationally driven action biases are beneficial in most situations, where they lead to appropriate responses. At times, however, the opposite behavioural strategy is required, for example, when obtaining a reward requires one to wait. In such cases, these biases can be maladaptive. Indeed, patients suffering from a range of psychiatric disorders appear to exhibit overly strong motivational biases. Neurally, (striatal) dopamine has been shown to play an important role in driving such biases, particularly in the appetitive domain. In contrast, we and others have shown a crucial role of frontal regions in controlling motivational biases when they are maladaptive.

In my talk, I will present recent progress on elucidating the relation of motivational biases to clinical neuropsychiatric symptom dimensions, using a large online population-based study in combination with computational modelling. For this, we adapted a well-established reinforcement learning paradigm that has been repeatedly shown to evoke motivational biases in decision making, for an online setting. I will then present pharmacological work examining the role of frontal dopamine in our ability to suppress maladaptive motivational biases in patients and healthy controls.

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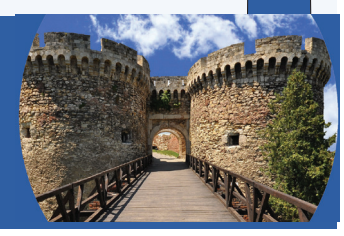

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Neuromodulation of brain states in health and disease: bridging experiments and computational models

Organizers: Srikanth Ramaswamy (Lausanne, CH)

A DATA-DRIVEN *IN SILICO* FRAMEWORK TO PREDICT CHOLINERGIC CONTROL OF NEOCORTICAL NETWORK STATES

Srikanth Ramaswamy, Cristina Colangelo

Blue Brain Project, École Polytechnique Fédérale de Lausanne (EPFL) Biotech Campus, Geneva, Switzerland

srikanth.ramaswamy@epfl.ch

Neuromodulators, such as acetylcholine (ACh), control information processing in neural microcircuits by regulating neuronal and synaptic physiology. Computational models and simulations enable predictions on the potential role of ACh in reconfiguring network activity. As a prelude into investigating how the cellular and synaptic effects of ACh collectively influence emergent network dynamics, we developed a data-driven framework incorporating phenomenological models of the physiology of cholinergic modulation of neocortical cells and synapses. The first-draft models were integrated into a biologically detailed tissue model of neocortical microcircuitry to investigate the effects of levels of ACh on diverse neuron types and synapses, and consequently on emergent network activity. Preliminary simulations from the framework, which was not tuned to reproduce any specific ACh-induced network effects, not only corroborate the long-standing notion that ACh desynchronizes spontaneous network activity, but also predict that a dose-dependent activation of ACh gives rise to a spectrum of neocortical network activity. We show that low levels of ACh, such as during non-rapid eye movement (nREM) sleep, drive microcircuit activity into slow oscillations and network synchrony, whereas high ACh concentrations, such as during wakefulness and REM sleep, govern fast oscillations and network asynchrony. In addition, spontaneous network activity modulated by ACh levels shape spike-time cross-correlations across distinct neuronal populations in strikingly different ways. These effects are likely due to the regulation of neurons and synapses caused by increasing levels of ACh, which enhances cellular excitability and decreases the efficacy of local synaptic transmission. We conclude by discussing future directions to refine the biological accuracy of the framework, which will extend its utility and foster the development of hypotheses to investigate the role of neuromodulators in neural information processing.

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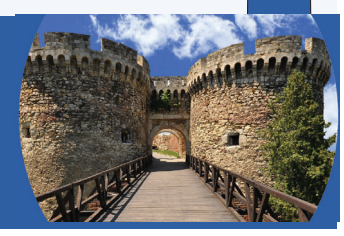

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Room Atlantic 2

SYMPOSIUM 13

THE ROLE OF STRESS AND INFLAMMATION IN PSYCHIATRIC DISORDERS

Organizers: Natasa Petronijevic (Belgrade, RS) and Nevena Radonjic (Syracuse, NY, USA)

NEUROINFLAMMATION IN PSYCHOTIC DISORDERS – RELEVANCE FOR SYMPTOMATOLOGY AND COGNITION

Sophie Erhardt

Dept of Physiology & Pharmacology, Karolinska Institutet, Stockholm, Sweden

sophie.erhardt@ki.se

Objective: Mounting evidence during the last decade has associated immune and inflammatory changes to psychosis and cognitive performance. Elevated levels of the pro-inflammatory cytokines interleukin (IL)-1β have been reported in both schizophrenia and bipolar disorder. Indeed, these cytokines also induce the kynurenine pathway of tryptophan degradation and patients with schizophrenia and bipolar disorder display elevated cerebrospinal fluid (CSF) concentrations of kynurenic acid (KYNA), an endogenous antagonist of N-methyl-D-aspartate (NMDA) and alpha7 nicotinic receptors.

In this presentation, data showing elevated brain kynurenic acid concentrations in patients with schizophrenia and patients with bipolar disorder and how kynurenic acid controls dopaminergic neurotransmission will be discussed.

Methods: CSF from patients with schizophrenia or bipolar disorder is analyzed for concentrations of cytokines and KYNA. Cytokines are analyzed with Mesoscale and KYNA is analyzed by HPLC.

Results: We will show that elevated brain levels of kynurenic acid relates to psychotic symptoms and cognitive impairments and furthermore, how the kynurenine pathway is highly inducible by immune activation. Another mechanism accounting for the abnormally high central kynurenine and kynurenic acid levels seen in schizophrenia, i.e. reduced expression and activity of the enzyme kynurenine 3-monooxygenase (KMO), hereby shunting the synthesis of kynurenine towards kynurenic acid, will be discussed. Indeed, expression and enzyme activity of KMO is reduced in schizophrenia. Pre-clinical results suggest that reduced synthesis of kynurenic acid by inhibition of kynurenine aminotransferase (KAT) II is a novel target for psychosis and may improve cognitive performance in schizophrenia. Here, we show that blockade of KAT II also decreases rat midbrain dopamine firing.

Conclusion: These studies point to an important role of KYNA in the development of schizophrenia and bipolar disorder. In particular, it is suggested that increased brain concentrations of KYNA are specifically associated with psychosis and impaired executive functions in humans. Experimental studies strongly support reduction of brain KYNA as a valuable pharmacological strategy in the treatment of these disorders.

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SYMPOSIUM 13

THE ROLE OF STRESS AND INFLAMMATION IN PSYCHIATRIC DISORDERS

Organizers: Natasa Petronijevic (Belgrade, RS) and Nevena Radonjic (Syracuse, NY, USA)

ACTIVATION OF INFLAMMASOME IN MAJOR DEPRESSION DISORDER

Gulderen Yanikkaya Demirel

Yeditepe University, Faculty of Medicine, Immunology Department, Istanbul, Turkey

gulderen.ydemirel@yeditepe.edu.tr

Inflammasomes are large protein complexes assembled to mediate the activation of caspase-1 which is responsible for secretion of pro-inflammatory cytokines IL-1β and IL-18. Besides IL-1β and IL-18 secretion, activation of inflammasome leads to pyropytosis, an inflammatory type of cell death. There are canonical and non-canonical types of inflammasomes, but up to date most studied one in Major Depression Disorder (MDD) is NOD like receptor pyrin containing 3 (NLRP3) which is also related to different innate immunity events such as infections, inflammation and autoimmunity. There are three main mechanisms that are effective for inflammasome activation: First one is generation of reactive oxygen species (ROS) which is associated with mitochondrial dysfunction, second is K+ efflux changes since high levels of ATP can activate the P2X7 purinergic receptor and reduce K+ levels. Third is the lysosomal rupture caused by the phagocytosis. Major Depressive Disorder is a psychiatric condition that affects up to 10% population worldwide. Besides the social burden this complex disease causes, the underlying mechanisms in order to develop effective therapy modalities is not known, clearly. In HUNT study performed in Norway, severe depression and anxiety symptoms were associated with moderately increased risk of blood stream infection, a prior disease to sepsis. Our collaborative studies and other researchers have shown that NLRP3 inflammasome is activated in different depression models in mice, and our collaborators have shown that an anesthetic drug (ketamine) can inactivate the inflammasome activity. Targeting inflammasome related suppression on individual basis can be a future therapeutic approach for precision medicine.

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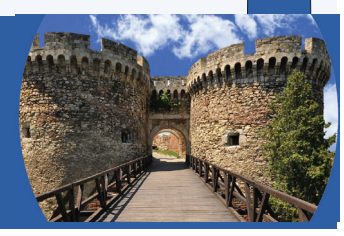

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SYMPOSIUM 13

THE ROLE OF STRESS AND INFLAMMATION IN PSYCHIATRIC DISORDERS

Organizers: Natasa Petronijevic (Belgrade, RS) and Nevena Radonjic (Syracuse, NY, USA)

ELEVATED KYNURENINE PATHWAY METABOLISM DURING NEURODEVELOPMENT: IMPLICATIONS FOR BRAIN AND BEHAVIOR

Ana Pocivavsek

Department of Pharmacology, Physiology, and Neuroscience, University of South Carolina School of Medicine, Columbia, South Carolina

ana.pocivavsek@uscmed.sc.edu

Dysfunction in the kynurenine pathway (KP) of tryptophan metabolism has been implicated in the pathology of schizophrenia (SZ). The KP metabolite kynurenic acid (KYNA), is an endogenous antagonist of α7 nicotinic acetylcholine (α7nACh) and N-methyl-D-aspartate (NMDA) receptors, and an activator of aryl hydrocarbon receptors (AhR). KYNA has been linked to cognitive impairments in SZ and may also contribute to sleep disturbances in patients. To further understand the role of KYNA in SZ etiology, we developed an experimental system in rats (Pocivavsek et al., Psychopharm., 2014) where kynurenine (kyn; 100 mg/day) is fed to pregnant Wistar dams from embryonic day (ED) 15 to ED 22 (control: ECon; kyn-treated: EKyn) to elevate KYNA in the fetal brain. As disturbances in sleep can often aggravate illness severity for SZ patients and plausible hypotheses suggest that cognitive deficits and abnormal sleep may be connected, in the present study we investigated the interplay between KP metabolism, sleep, and cognition. To this end, we assessed: 1) KP metabolism during the light (ZT6) and dark phase (ZT18); 2) sleep-wake behavior during both; 3) spatial learning and memory phases in male and female adult (postnatal day 56 -85) offspring from ECon and EKyn litters. Cortical KYNA levels were increased (+128%) at ZT6 in male, but not female, EKyn compared to ECon (**P<0.01). No differences were found at ZT18. Adult offspring were implanted with telemetric devices to acquire polysomnographic recordings to combine electroencephalogram (EEG) and electromyogram (EMG) readings (N=6-8 per group). Analyses of vigilance state parameters categorized as wake, rapid eye movement (REM) and non-REM (NREM) were assessed. Our findings indicate distinct sex differences in sleep disturbances among ECon and EKyn offspring. EKyn males had significantly less REM duration during the light phase (*P<0.05, -21%). EKyn females had less frequent wake bouts (*P<0.05, -30%), which were also longer in duration (***P<0.001, +37.5%), and less frequent NREM bouts (*P<0.05, -28%) during the dark phase. In separate animals, we tested spatial learning and memory in the Barnes maze. Male EKyn offspring displayed impairments, evidenced as increased latency to find the escape box, across the acquisition trials (P < 0.05). During a reversal trial, EKyn offspring were significantly impaired, taking longer to find the new escape box (P<0.05) and entering the previous escape box location more frequently than ECon offspring (P<0.001). Together our data demonstrate a striking sex- and light phase-dependent increase in cortical KYNA and sleep alterations in EKyn offspring. We are continuing to investigate elevated prenatal kynurenine exposure to further understand the interplay between KP metabolism in psychiatric illness, sleep disturbances, and cognitive outcomes.

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Room Atlantic 2

Symposium 13

The role of stress and inflammation in psychiatric disorders

Organizers: Natasa Petronijevic (Belgrade, RS) and Nevena Radonjic (Syracuse, NY, USA)

STRESS AND INFLAMMATION IN ANIMAL MODELS OF PSYCHIATRIC DISORDERS

Natasa Petronijević

Institute of Clinical and Medical Biochemistry, School of Medicine, University of Belgrade, Pasterova 2, Belgrade, Serbia

natasapetronijevic@yahoo.com

Inflammation and dysregulation of hypothalamic–pituitary–adrenal (HPA) axis are described in schizophrenia (SCH). Long-term treatment with antipsychotics is often required for disease control. Perinatal phencyclidine (PCP) administration to rodents represents an animal model of SCH. The aim of this study was to assess the effects of different antipsychotics on the HPA axes and cytokine levels and its relation to bone and metabolic changes in rats perinatally treated with PCP.

Male Wistar rats were subcutaneously treated on 2nd, 6th, 9th and 12th postnatal day (PN), with either PCP or saline. Antipsychotics were apllied from PN35. Dual X-ray absorptiometry measurements were performed on PN98. Animals were sacrificed on PN100. Concentrations of corticosterone, TNF-α and IL-6 were measured in the serum using ELISA kits. Expressions of the glucocorticoid receptor (GR), phosphorilated GR (pGR), chaperone and co-chaperone proteins and the expression of markers of autophagy and apoptosis in the brain of adult rats were assessed by Western blot. Perinatal PCP administration caused a significant decrease in bone mass and deterioration in bone quality. Interleukine and corticosterone consentrations were unchanged but increased sensitivity of GR signaling system was detected. Haloperidol had deleterious, while clozapine had protective effect on bones. Both haloperidol and clozapine caused decrease of the sensitivity of GR signaling system but clozapine caused significant increase of corticosterone and TNF-α concentrations. Perinatal PCP administration and chronic antipsychotic administration have affected apoptosis and autophagy processes. Taken together our results indicate that haloperidol affects bones while clozapine alters HPA axes and inflammatory markers.

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8:30–10:10

Room Pacific

Symposium 01

Cellular signaling and quality control mechanisms in neurodegeneration

Organizers: Simone Engelender (Haifa, IL) and Tiago Outeiro (Waldweg, DE)

TARGETING NEUROINFLAMMATION FOR THE TREATMENT OF PSYCHIATRIC DISORDERS: FROM PRECLINICAL PERSPECTIVE

Feyza Arıcıoğlu

Pharmacology Department and Psychopharmacology Research Unit, School of Pharmacy, Marmara University, Istanbul, Turkey

faricioglu@marmara.edu.tr

At present, the pathophysiology of many psychiatric disorders is still not fully understood. Current treatment approaches that have been used in psychiatric disorders for many years and usually have a single mechanism-based effect are inadequate to control disease symptoms; modulation of dopamine in schizophrenia and monoamines for depression. Patients who do not respond to the current treatment options in the majority of psychiatric disorders, mainly diseases such as depression affecting 10% of the population and schizophrenia affecting 1% and resistance cases constitute about 1/3 of them. Recent studies indicate that the increase in neuroinflammatory proinflammatory cytokines is a common pathology in the development of these diseases. Uncontrolled astrocyte/glia activity increases proinflammatory cytokines, causes changes in the levels of neurotransmitters and thus leads to a decrease in neurotrophic factors. This form of neuroplasticity suppresses the ability of the synapses to change, to be structurally and functionally adaptive to certain situations. Treatment is expected to increase the production of neuronal plasticity and neurotrophic factors, including hippocampal neurons, synaptogenesis and neuronal maturation. A growing number of evidences have put forward that stress, depression and schizophrenia are associated with the over-activation of immune-inflammatory pathways. There have been few but encouraging reports suggesting that agmatine, an endogenous molecule widely distributed in brain, might be a novel therapeutic candidate targeted at inflammatory aspect of depression. Current research findings from validated animal model studies promising a therapeutic value of agmatine on enhancement on neurotrophic support, molecular and/or antiinflammatory properties besides behavioural effects.

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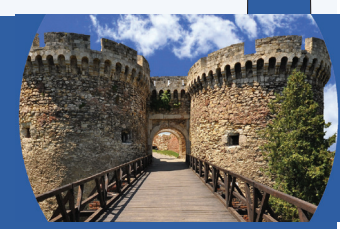

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Room Mediterranean

SYMPOSIUM 14

EXPLORING NOVEL THERAPEUTIC APPROACHES FOR PAIN DISORDERS

Organizers: Slobodan M. Todorovic (Aurora, CO, USA) and Sonja Vuckovic (Belgrade, RS)

MOLECULAR MECHANISMS OF T-TYPE CALCIUM CHANNELS PLASTICITY IN PAINFUL DIABETIC NEUROPATHY

Slobodan M. Todorovic, Sonja LJ. Joksimovic, Vesna Jevtovic-Todorovic

Department of Anesthesiology, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA

slobodan.todorovic@ucdenver.edu

Aims: Our recent studies have implicated plasticity of the Cav3.2 isoform of T-type Ca^{2+} channels in the development of painful peripheral diabetic neuropathy (PDN). Here we investigated if glycosylation of Cav3.2 channels *in vivo* may contribute to the development of painful PDN in Type I diabetes.

Methods: We used immunoprecipitation of native Cav3.2 channels and gel-shift analysis with tissues exposed to PNGase-F to investigate if glycosylation occurs in native dorsal root ganglion (DRG) tissues. For pain studies we injected another inhibitor of glycosylation, neuraminidase (NEU) intra-plantary (i.pl.) into peripheral receptive fields of sensory neurons and measured heat sensitivity and mechanical sensitivity of healthy mice and mice with streptazocin (STZ)-induced painful PDN.

Results: We found that N-terminal fragments of native $Ca_V3.2$ channels in DRGs are glycosylated to a greater extent in diabetic than in the healthy animals. We also found that injections of NEU, but not vehicle, completely reversed thermal and mechanical hyperalgesia in diabetic WT mice. In contrast, NEU did not affect baseline thermal and mechanical sensitivity in diabetic Cav3.2 KO mice which were resistant to the development of painful PDN.

Conclusion: Our results demonstrate that glycosylation-induced alterations in Cav3.2 can contribute to hyperalgesia in PDN and that inhibitors of glycosylation can be used to ameliorate painful symptoms in Type 1 diabetes.

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SYMPOSIUM 14

EXPLORING NOVEL THERAPEUTIC APPROACHES FOR PAIN DISORDERS

Organizers: Slobodan M. Todorovic (Aurora, CO, USA) and Sonja Vuckovic (Belgrade, RS)

THE ROLE OF GABAA RECEPTORS IN CHRONIC NEUROPATHIC PAIN AFTER TRAUMATIC NERVE INJURY

Vesna Jevtovic-Todorovic, Aleksandar Lj. Obradovic, Joseph Scarpa, Slobodan M. Todorovic

Department of Anesthesiology, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA

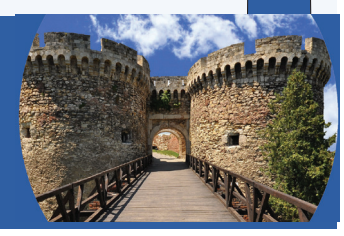
vesna.jevtovic-todorovic@ucdenver.edu

Introduction: Drugs that promote γ-aminobutyric acid (GABA) activity in the spinal cord may provide partial relief of neuropathic pain (NPP) symptoms. We examined here how in vivo silencing of the GABA receptor type A (GABAA) α2 gene in dorsal root ganglia (DRG) may affect NPP after sciatic nerve crush injury.

Methods: After crush injury to the right sciatic nerve of female rats, the α2 GABAA antisense or mismatch oligodeoxynucleotides, or NO-711 (a GABA uptake inhibitor) were applied directly to the L5 DRG. In vivo behavioral assessment of nociception was conducted before the injury and ensuing 10 days. In vitro quantification of α2 GABAA protein and electrophysiological studies of GABAA currents were performed on acutely dissociated L5 DRG neurons at relevant time points.

Results: Development of NPP in adult female rats coincides with significant down-regulation of the α2 subunit expression in the ipsilateral DRG (about 30%). Selective down-regulation of α2 expression in DRGs worsened mechanical and thermal hypersensitivity in crush-injured animals and caused development of significant mechanical and thermal hypersensitivity in sham animals. Conversely, up-regulation of endogenous GABA via blockade of its uptake in DRG alleviated NPP.

Conclusion: The GABAA receptor in the DRG plays an important role in pathophysiology of NPP caused by sciatic nerve injury and represents promising target for novel pain therapies.



MECHANISM OF CENTRAL SENSITIZATION AND NEURO-GLIA INTERACTIONS IN THE PASSIVE TRANSFER-TRAUMA MOUSE MODEL OF COMPLEX REGIONAL PAIN SYNDROME

Zsuzsanna Helyes[1,4], Valéria Tékus[1], Nikolett Szentes[1], Krisztina Pohóczky[1,9], Bálint Botz[1], Tamás Kiss[1], Ágnes Kemény[1], Zsuzsanna Környei[2], Krisztina Tóth[2], Nikolett Lénárt[2], Hajnalka Ábrahám[3], Emmanuel Pinteaux [5], Sheila Francis[6], Serena Sensi[7], Ádám Dénes[2] and Andreas Goebel[7,8]

1Department of Pharmacology and Pharmacotherapy, Medical School;
János Szentágothai Research Centre & Centre for Neuroscience, University of Pécs, Hungary;
2Momentum Laboratory of Neuroimmunology, Institute of Experimental Medicine, Budapest, Hungary;
3Department of Biology and Electron Microscopy, Medical School, University of Pécs, Hungary;
4PharmInVivo Ltd., Pécs, Hungary;
5Division of Neuroscience and Experimental Psychology, Faculty of Biology, Medicine, and Health. University of Manchester, Manchester, UK;
6Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK;
7Department of Translational Medicine, University of Liverpool, UK;
8The Walton Centre NHS Foundation Trust, Liverpool, UK;
9Department of Pharmacology, Faculty of Pharmacy, University of Pécs, Hungary

zsuzsanna.helyes@aok.pte.hu

Neuro-immune interactions contribute to severe pain and inflammatory signs in Complex Regional Pain Syndrome (CRPS). However, the pathophysiological mechanisms remain unclear and therapies are unsatisfactory.

Here we investigated central and peripheral immune mechanisms in a passive transfer-trauma translational mouse model of CRPS, where small plantar skin-muscle incision was performed in female C57Bl/6 mice treated daily with purified serum-IgG from patients with longstanding CRPS, or healthy volunteers during a period of 3-14 days. Microglia in pain-related central nervous system regions, as well as edema, hyperalgesia, inflammatory signs, sensory neuropeptides and cytokines in the paw were investigated.

CRPS IgG significantly increased and prolonged swelling and mechanical hyperalgesia of the incised paw compared to IgG from healthy controls. Following a short-lasting inflammatory response with oedema, substance P and inflammatory cytokine increase, CRPS IgG-injected mice displayed enhanced hyperalgesia together with sustained, profound microglia and astrocyte activation in the spinal dorsal horn, periaqueductal grey and somatosensory cortex, indicating central sensitization. Deletion of interleukin-1 (IL-1) and perioperative IL-1 receptor 1 (IL-1R1) blockade with anakinra, but not treatment with the glucocorticoid prednisolone, precluded these changes. Anakinra initiated 8 days after incision also abrogated sensitization. Furthermore, with a novel IL-1beta floxed$^{(fl/fl)}$ mouse line, we demonstrated that CRPS IgG-induced changes are in part mediated by microglia-derived IL-1beta, suggesting that neuroinflammation contributes to the transferred CRPS phenotype.

These results indicate that persistent CRPS is often contributed to autoantibodies and highlight a novel therapeutic use for clinically licensed antagonists, such as anakinra, to prevent or treat CRPS via blocking IL-1 actions.

Funding: National Brain Research Program 2017-1.2.1-NKP-2017-00002 GINOP-2.3.2-15-2016-00050 (PEPSYS), EFOP 3.6.2-17-2017-00008 N (2017-2019)

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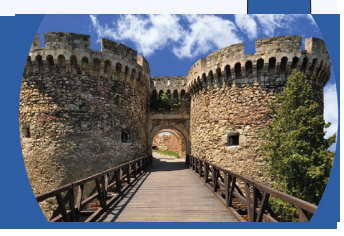

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Room Mediterranean

SYMPOSIUM 14

EXPLORING NOVEL THERAPEUTIC APPROACHES FOR PAIN DISORDERS

Organizers: Slobodan M. Todorovic (Aurora, CO, USA) and Sonja Vuckovic (Belgrade, RS)

EVIDENCE FOR THE INVOLVEMENT OF NITRIC OXIDE IN THE ANTINOCICEPTIVE EFFECT OF MAGNESIUM

S. Vuckovic, D. Srebro, K. Savic Vujovic, M. Prostran

Department of Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

vuckovicsonja1@gmail.com

Aim of Investigation: Magnesium belongs to antagonists of N-methyl-D-aspartate receptors. Previously, we showed that systemic magnesium sulfate is effective against inflammatory pain in rats. This study is aimed at evaluating whether nitric oxide is involved in the analgesic action of magnesium sulfate in rats.

Methods: In male Wistar rats, two models of inflammatory pain were used: the acetic acid - induced writhing test and the carrageenan - induced mechanical hyperalgesia. After injection of carrageenan (0.5%, 0.1 ml) into the hind paw, paw withdrawal threshold was measured by electronic von Frey apparatus. Magnesium sulfate was administered subcutaneously (s.c.) with/without intraperitonealy (i.p.) tested inhibitors of the nitric oxide synthase.

Results: In carrageenan – induced hyperalgesia, S-methylisothiourea (SMT; 0.015 mg/kg, i.p.), a selective inhibitor of inducible nitric oxide synthase, and N-ω-Propyl-L-arginine hydrochloride (L-NPA; 1 and 2 mg/kg, i.p.), a selective inhibitor of neuronal nitric oxide synthase, decrease the analgesic effect of magnesium sulfate (5 mg/kg, s.c.). In acetic-acid – induced writhing test in rats, the antinociceptive effect of magnesium sulfate (15 mg/kg, s.c.) does not change in the presence of L-NPA (2 and 10 mg/kg, i.p.) or SMT (0.015 and 10 mg/kg, i.p.)

Conclusions: Nitric oxide produced by neuronal and inducible nitric oxide synthase modulates the analgesic effects of magnesium sulfate in the somatic, but not in the visceral inflammatory model of pain in rats.

This work was supported by the Ministry of Education, Science and Technological Development of Serbia (Grant No. 175023).

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Room Mediterranean

SYMPOSIUM 14

EXPLORING NOVEL THERAPEUTIC APPROACHES FOR PAIN DISORDERS

Organizers: Slobodan M. Todorovic (Aurora, CO, USA) and Sonja Vuckovic (Belgrade, RS)

THE PAIN TARGET, TRESK REGULATES SCN NOCTURNAL MEMBRANE POTENTIAL AND CA^{2+} DYNAMICS

Tatjana Lalic[1], Aiste Steponenaite[2], Farid Ebrahimjee[3], Liting Wei[1], Sridhar Vasudevan[3], Stuart Peirson[1], Gurprit Lall[2], Zameel Cader[1]

1 Nuffield Department of Clinical Neurosciences, Weatherall Institute for Molecular Medicine, John Radcliffe Hospital, University of Oxford, Oxford, UK;
2 Medway School of Pharmacy, University of Kent, Chatham, UK;
3 Pharmacology Department, University of Oxford, Oxford, UK

tatjana.lalic@ndcn.ox.ac.uk

Physiological and behavioural daily rhythms depend on the cell-autonomous generation of circadian time by the suprachiasmatic nucleus (SCN) through the fine control of the molecular clock. The SCN may also regulate pain behaviours, which has previously been shown to display diurnal patterns. Organisation of the SCN circuit and how it's outputs might affect nociception and sensory thresholds is poorly understood.

The two-pore (K2P) potassium channel, TWIK-related spinal cord potassium channel (TRESK, encoded by KCNK18), has been suggested in the pathogenesis of migraine and pain. TRESK is strongly expressed in the nociceptors and we now find is highly enriched K2P in the SCN compared to other brain regions. We sought to further investigate the role of TRESK in SCN function using wildtype and knock-out mice.

We found that TRESK has a circadian variation in expression, with higher levels during the night. Loss of TRESK results in loss of nocturnal hyperpolarisation and diurnal variation in spontaneous firing is significantly reduced. Both glutamate and light responses produced drastic alteration in cellular phenotypes of the SCN, which is likely due to changes in the basal [Ca2+]i, and corresponding behavioural phase shift deficiencies.

We therefore demonstrate that TRESK is important for the correct cellular responses of the SCN, which then has implications for regulation of the SCN output and may also be relevant in pain mechanisms.

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Room Baltic

Symposium 15

What can we learn from animal models of stress and Alzheimer's disease?

Organizers: Nela Puškaš (Belgrade, RS) and Christina Dalla (Athens, GR)

SEX DIFFERENCES IN STRESS ANIMAL MODELS: FROM BEHAVIOR TO NEUROPLASTICITY

Nikolaos Kokras[1,2] and Christina Dalla[1]

1Dep. of Pharmacology, Medical School, National & Kapodistrian University of Athens, Greece;
2First Department of Psychiatry, Eginition Hospital, National and Kapodistrian University of Athens, Greece

nkokras@med.uoa.gr

Women are more vulnerable than men in most stress-related neuropsychiatric disorders. Moreover, recent preclinical findings link estrogens' signaling with mood and cognition. Our group has studied preclinical sex differences in stress models of depression [1, 2]. Furthermore, we have investigated the behavioral and neurochemical effects of estrogen depletion by aromatase inhibition in male and female rats exposed to forced swim test. We have demonstrated that treatment with letrozole, which is an aromatase inhibitor, decreases noradrenaline levels and dopaminergic ratio in the hippocampus and prefrontal cortex of male and female rats. Also, it enhances the serotonergic ratio in the hippocampus of males and females [3]. Finally, we have recently shown that the integrity of the circuit hippocampus – prefrontal cortex is necessary for stress-induced deficits in neuroplasticity indices and for the expression of "depressive" behaviors [4]. Overall, our studies highlight the importance of inclusion of both male and female animals in preclinical neuroscience research and implicate the critical role of the hippocampal-cortical circuit in stress response.

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2. Kokras, N., et al., *Forced swim test: What about females?* Neuropharmacology, 2015. **99**: p. 408-21.
3. Kokras, N., et al., *Sex differences in behavioral and neurochemical effects of gonadectomy and aromatase inhibition in rats.* Psychoneuroendocrinology, 2018. **87**: p. 93-107.
4. Kafetzopoulos, V., et al., *The nucleus reuniens: a key node in the neurocircuitry of stress and depression.* Mol Psychiatry, 2018. **23**(3): p. 579-586.

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SEED-INDUCED AB DEPOSITION IMPAIRS ADULT NEUROGENESIS IN 5XFAD MICE

Melanie Meyer-Luehmann[1,2]

1Department of Neurology, Medical Center – University of Freiburg, Freiburg, Germany;
2Faculty of Medicine, University of Freiburg, Freiburg, Germany.

melanie.meyer-luehmann@uniklinik-freiburg.de

Alzheimer´s disease (AD) is characterized by severe neuronal loss as well as the accumulation of amyloid-β (Aβ) which ultimately leads to plaque formation. These Aβ deposits can be induced in young pre-depositing APP transgenic mice by intracerebral injection of Aβ-containing brain homogenate. Although a decline of neurogenic capacity in the brain of AD patients and AD mouse models has been reported, our understanding of whether this impairment is specifically altered by Aβ plaques is limited. Here, we find that induced Aβ deposition (Aβ seeding), representing early stages of plaque formation, leads to a dramatic decrease in adult neurogenesis in the hippocampus and olfactory bulb. We further report that the generation and maturation of newborn neurons is affected by the induction of Aβ deposition in both neurogenic niches, the SVZ and SGZ, resulting in an excitatory/inhibitory synaptic imbalance in the GCL. Notably, cell death and apoptosis occur in conjunction with Aβ seeding and the exposure to enriched environment and voluntary running reduces Aβ seeding via activated microglia and vivifies neurogenesis and proliferation.

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WHAT CAN WE LEARN FROM ANIMAL MODELS OF STRESS AND ALZHEIMER'S DISEASE?

Organizers: Nela Puškaš (Belgrade, RS) and Christina Dalla (Athens, GR)

DYSREGULATION OF AUTOPHAGY AND STRESS GRANULE-RELATED PROTEINS IN STRESS-DRIVEN TAU PATHOLOGY

Joana Margarida Silva[1,2], Sara Rodrigues[1,2], Akihiko Takashima[3], Benjamin Wolozin[4], Nuno Sousa[1,2], Ioannis Sotiropoulos[1,2]

1 Life and Health Sciences Research Institute (ICVS), Medical School, University of Minho, Campus Gualtar, Braga, Portugal;
2 ICVS/3B's - PT Government Associate Laboratory, Braga/Guimarães, Portugal;
3 Department of Life Science, Faculty of Science, Gakushuin University, Tokyo, Japan;
4 Department of Pharmacology & Experimental Therapeutics, School of Medicine, Boston University, MA, Boston, USA

joanamsilva@med.uminho.pt

Aim: Imbalance of neuronal proteostasis associated with misfolding and aggregation of Tau protein is a common neurodegenerative feature in Alzheimer' s disease (AD) and other Tauopathies. Consistent with suggestions that lifetime stress may be an important AD precipitating factor, we previously reported that environmental stress and high glucocorticoid (GC) levels induce accumulation of aggregated Tau; however, the molecular mechanisms for such process remain unclear. Herein, we monitor a novel interplay between RNA-binding proteins (RBPs) and autophagic machinery in the underlying mechanisms through which chronic stress and high GC levels impact on Tau proteostasis precipitating Tau aggregation.

Methods & results: Using molecular, pharmacological and behavioral analysis, we demonstrate that chronic stress and high GC trigger mTORdependent inhibition of autophagy, leading to accumulation of Tau aggregates and cell death in P301L-Tau expressing mice and cells. In parallel, we found that environmental stress and GC disturb cellular homeostasis and trigger the insoluble accumulation of different RBPs, such as PABP, G3BP1, TIA-1, and FUS, shown to form stress granules (SGs) and Tau aggregation. Interestingly, an mTOR-driven pharmacological stimulation of autophagy attenuates the GC-driven accumulation of Tau and SG-related proteins as well as the related cell death, suggesting a critical interface between autophagy and the response of the SG-related protein in the neurodegenerative potential of chronic stress and GC.

Conclusion: These studies provide novel insights into the RNA– protein intracellular signaling regulating the precipitating role of environmental stress and GC on Tau-driven brain pathology.

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Organizers: Nela Puškaš (Belgrade, RS) and Christina Dalla (Athens, GR)

IMPAIRMENTS OF HIPPOCAMPAL NEUROGENESIS IN MOUSE MODEL OF ALZHEIMER'S DISEASE

Nela Puškaš[1], Ivan Zaletel[1], Marija Schwirtlich[2], Milka Perović[3], Milena Stevanović[2,4,5], Selma Kanazir[3]

1Institute of Histology and Embryology "Aleksandar Đ. Kostić", School of Medicine, University of Belgrade, Belgrade, Serbia;
2Laboratory for Human Molecular Genetics, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Belgrade, Serbia;
3Institute for Biological Research "Siniša Stanković", University of Belgrade, Belgrade, Serbia;
4University of Belgrade, Faculty of Biology, Belgrade, Serbia;
5Serbian Academy of Sciences and Arts, Belgrade, Serbia.

nela@dr.com

Alzheimer's disease (AD) is the most common form of senile dementia among elderly with sex-biased epidemiological profile. Impairments of neurogenesis in the subgranular zone (SGZ) of the hippocampal dentate gyrus has been related to cognitive deficits and memory loss in AD. Members of *B* group of Sry-related *Sox* family of transcription factors govern diverse cellular processes in the brain during development and play critical roles in regulating neurogenesis in embryonic and adult nervous system. The aim of the present study was to evaluate the expression pattern of SOXB proteins in SGZ in the 5xFAD transgenic mouse model of AD of both genders that rapidly develops severe amyloid pathology. Immunohistochemical analysis showed a significant decrease in the number of cells expressing Sox1, Sox2 and Sox21 transcription factors throughout the SGZ of 8 weeks old 5xFAD transgenic mouse model of AD in comparison to their non-transgenic counterparts. Despite observed changes in expressional pattern of examined Sox proteins, the proliferative capacity evaluated by the number of Ki-67-immunoreactive cells remained unaffected in transgenic mice of both genders. Differences in SOXB protein expression coincidence with reduced number of doublecortin (DCX) immunoreactive immature neurons found in Tg males, but not in females. Based on our results we can conclude that SOXB proteins might be considered as new biomarkers in research for detection of early impairments in adult neurogenesis and that there are gender-specificities in DCX-immunoreactivity related to surviving period and differentiation of immature neuron. The cause of this sex difference has yet to be elucidated.

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WHAT CAN WE LEARN FROM ANIMAL MODELS OF STRESS AND ALZHEIMER'S DISEASE?

Organizers: Nela Puškaš (Belgrade, RS) and Christina Dalla (Athens, GR)

FOOD RESTRICTION EXACERBATES INFLAMMATION AND NEURONAL DEFICITS IN MOUSE MODEL OF ALZHEIMER'S DISEASE

Milka Perovic[1], Divna Lazic[2], Vesna Tesic[1], Desanka Milanovic[1], Selma Kanazir[1]

1Laboratory for Molecular Neurobiology, Department of Neurobiology, Institute for Biological Research for Biological Research, University of Belgrade, Serbia;
2Zilkha Neurogenetic Institute, Keck School of Medicine, University of Southern California, Los Angeles, California, USA

milkap@ibiss.bg.ac.rs

Food restriction (FR) is known for its beneficial effects on age-related changes and associated disorders, like Alzheimer's disease (AD). However, the literature on the effects of food restriction on aging- or pathology-related cognitive decline is controversial, emphasizing the importance of the type, onset and duration of food restriction. In the present study, we assessed the effects of preventive every-other-day feeding regimen on neurodegenerative phenotype in 5XFAD transgenic mice, a commonly used mouse model of Alzheimer's disease.

Every-other-day feeding regimen was introduced to transgenic female mice at the age of 2 months and the effects on amyloid-β (Aβ) accumulation, gliosis, synaptic plasticity, and blood-brain barrier breakdown were analyzed in cortical tissue of 6-month-old animals.

Every-other-day feeding significantly increased inflammation in the cortex, reflected by the expression of microglial and astrocytic markers. Increase in gliosis was accompanied with downregulation of synaptic plasticity proteins, neuritic dystrophy and neuronal cell loss. However, every-other-day feeding regimen did not affect Aβ load and blood-brain barrier permeability in the cortex of 5XFAD mice.

Our results demonstrate that EOD feeding regimen exacerbates Alzheimer's disease-like neurodegenerative changes, suggesting that caution should be made when using food restriction in prodromal phase of this neurodegenerative disease.

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Room Pacific

Symposium 16

Imaging of the nervous system across different scales – from neuronal networks to single molecules

Organizers: Petar Marinković (Munich, DE) and Ivana Nikić-Spiegel (Tübingen, Germany)

MAY THE FORCE BE WITH YOU: MITOCHONDRIAL LIFE IN THE NERVOUS SYSTEM

Thomas Misgeld

Institute of Neuronal Cell Biology, Technical University of Munich & DZNE, Munich, Germany

thomas.misgeld@tum.de

In this presentation, I will discuss my lab's recent and ongoing work on the in vivo dynamics and diversity of mitochondria in the nervous system. I will present work on how the mitochondrial life cycle maps onto the extended geometry of neurons – and especially focus on the question, where in motor neurons mitochondria are dismantled, and how such mitochondrial degradation is compartmentalized. Moreover, I will discuss a new approach to study the molecular and functional diversity of mitochondria between cells in the nervous system, which can aid our understanding of metabolic specialization amongst neural cell types.

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IN VIVO IMAGING REVEALS REDUCED ACTIVITY OF NEURONAL CIRCUITS IN A MOUSE TAUOPATHY MODEL

Petar Marinković[1,2,3,4], Sonja Blumenstock[2,3,4], Pieter M Goltstein[5], Viktoria Korzhova[1,2], Finn Peters[2,3,4], Andreas Knebl[2,4] and Jochen Herms[2,3,4]

1Department of Pharmacy, Ludwig-Maximilians-University Munich, Munich, Germany;
2Department for Translational Brain Research, German Center for Neurodegenerative Diseases (DZNE), Munich, Germany;
3Munich Cluster of Systems Neurology (SyNergy), Ludwig-Maximilians-University Munich, Munich, Germany;
4Center for Neuropathology and Prion Research, Ludwig-Maximilians-University Munich, Munich, Germany;
5Max Planck Institute of Neurobiology, Martinsried, Germany

petar.marinkovic@cup.lmu.de

Pathological alterations of tau protein play a significant role in the emergence and progression of neurodegenerative disorders. Tauopathies are characterized by detachment of the tau protein from neuronal microtubules, and its subsequent aberrant hyperphosphorylation, aggregation and cellular distribution. The exact nature of tau protein species causing neuronal malfunction and degeneration is still unknown. In the present study, we used mice transgenic for human tau with the frontotemporal dementia with Parkinsonism-associated P301S mutation. These mice are prone to develop fibrillar tau inclusions, especially in the spinal cord and brainstem. In the same time, cortical neurons are not so strongly affected by fibrillar but rather by soluble tau forms. We took advantage of the possibility to induce formation of neurofibrillary tangles (NFTs) in a subset of these cortical neurons by local injection of preformed synthetic tau fibrils. By using chronic *in vivo* two-photon calcium imaging in awake mice we were able for the first time to follow the activity of individual NFT–bearing and compare it to the activity of NFT–free neurons over disease course. Our results revealed strong reduction of calcium transients' frequency in layer 2/3 cortical neurons of P301S mice, independent of NFT presence. These results clearly point to the impairing role of soluble, mutated tau protein species present in the majority of the neurons investigated in this study.

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IN VIVO PATHOGENESIS OF AUTOIMMUNE WHITE AND GRAY MATTER DAMAGE

Martin Kerschensteiner

Institute of Clinical Neuroimmunology, Ludwig-Maximilians University Munich, Germany

Martin.Kerschensteiner@med.uni-muenchen.de

Here, I want to discuss how advances in in vivo microscopy can improve our understanding of the cellular, subcellular and molecular mechanisms that mediate inflammatory damage to neurons. Immune-mediated damage to neurons plays a crucial role in inflammatory diseases of the central nervous system (CNS) like multiple sclerosis (MS), as we know by now that the extend of neuronal damage critically determines the clinical disability of MS patients. However we still understand very little about the processes that initiate damage to neurons, their axons or their synapses. In my presentation I will summarize our recent work that uses in vivo microscopy techniques to unravel (i) how axons are damaged in inflammatory white matter lesions that dominate the early, relapsing-remitting phase of MS and (ii) how synapses become the target of an inflammatory attack in gray matter lesions that characterize the advanced, progressive phase of the disease. Using these examples, I hope to illustrate how recent advances in light microscopy can help us to reveal and mechanistically dissect the interactions of activated immune cells and neurons as they happen in the living CNS.

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Imaging of the nervous system across different scales – from neuronal networks to single molecules

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IMAGING AXONAL INJURY WITH NANOSCALE RESOLUTION

Ivana Nikić-Spiegel

Werner Reichardt Centre for Integrative Neuroscience, University of Tübingen, Tübingen, Germany

ivana.nikic@uni-tuebingen.de

Development of super-resolution microscopy techniques has changed the limits of light microscopy resolution from 200nm to less than 20nm. This allows us to see biological processes with unprecedented spatial resolution and near-molecular-level of detail. For example, axons have a very unique cytoskeletal organisation that is only visible with super-resolution microscopy. As a result of this, we learned about the nanoscale architecture of healthy axons in vitro. However, we do not know what happens during axonal injury. My laboratory studies this in a model of oxidative stress-induced injury. Imaging with nanoscale resolution will provide us with novel insights in molecular changes during axonal injury. However, to capture biological dynamics with high spatiotemporal resolution requires not only an advancement in imaging, but also an advancement in labelling technologies. In this regard, my laboratory has developed novel live cell minimal labelling tags. Our tags are based on single amino acids and are thus particularly suitable for super-resolution microscopy, as will be discussed in my presentation.

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SYMPOSIUM 17

MOLECULAR BASIS OF NEURODEGENERATION

Organizers: Boris Rogelj (Ljubljana, SI) and Tibor Hortobagyi (Szeged, HU)

PERTURBED NUCLEOCYTOPLASMIC SHUTTLING IN ALS AND FTD

Boris Rogelj[1,2,3]

1Department of Biotechnology, Jožef Stefan Institute, Ljubljana, Slovenia;
2Biomedical Research Institute BRIS, Ljubljana, Slovenia;
3Faculty of Chemistry and Chemical Technology, University of Ljubljana, Ljubljana, Slovenia

boris.rogelj@ijs.si

Aims: Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are devastating neurodegenerative diseases that form two ends of a complex disease spectrum. Cytoplasmic mislocalization and aggregation of nuclear RNA binding proteins (RBPs) is one of the hallmark pathological features of ALS and FTD, and suggests perturbance of nuclear transport mechanisms in their aetiology. In order to understand the disease process and look for ways of treatment, discerning pathways that may bring about the mislocalization and aggregation of TDP-43 and FUS is one of the main focuses of our research. Determination of in vivo protein-protein interaction of RBPs, will also provide far wider insight in general molecular process occurring in cell nuclei.

Methods: Using in vivo interactome capture approaches, we are looking at the changes in binding partners of FUS and TDP-43 when they are mislocalized and/or aggregated. We are also looking at the effects of post translational modifications on mislocalization of these proteins.

Results: We have found that nuclear localization of these proteins leads to interactions with proteins associated with transcriptional regulation, splicing and translational repression. In the cytoplasm interaction partners were found to be part of cytoplasmic stress granules (SG) and P-bodies and associated with translational repression or degradation of the mRNA molecules.

Conclusions: Pathological cytoplasmic mislocalization may involve loss of regulatory functions associated with transcription on one hand. On the other hand, the increased association of cytoplasmic FUS/TDP-43 with SG and P-bodies suggests the possible role of these granules in the mechanism of neurodegeneration.

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SYMPOSIUM 17

MOLECULAR BASIS OF NEURODEGENERATION

Organizers: Boris Rogelj (Ljubljana, SI) and Tibor Hortobagyi (Szeged, HU)

WHAT IS KNOWN ABOUT AMYLOID-PORE STRUCTURE AND COMMON DOWN-STREAM PROCESSES

Eva Žerovnik

Department of Biochemistry and Molecular and Structural Biology, Jožef Stefan Institute, Ljubljana Slovenia

eva.zerovnik@ijs.si

The range of diseases which fall under "proteinopathies" broadens, ranging from neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, various dementias to progressive myoclonus epilepsies and neuropsychiatric conditions, such as schizophrenia. Protein aggregation due to intrinsic and extrinsic factors is a common denominator. The mechanism of protein aggregation to amyloid fibrils is being studied in order to determine points for pharmacological intervention. It has been agreed that some form of the oligomeric intermediates prior to formation of amyloid fibrils interact with cellular membranes or even make pores, suggesting a common mechanism of toxicity and regulation of proteostasis. I will present "amyloid pore" hypothesis that any mis-folded and aggregating protein in the cytosol may behave in a similar way and that prefibrillar oligomers may bind to membranes (mitochondrial, lysosomal, etc…) or even perforate them. I will go further, suggesting that this might not only cause toxicity but could also be a signal to recruit cell's defense systems to misfolded proteins. In order to come closer to understand the amyloid toxicity, we will study a model intracellular protein (stefin B), whose oligomers and protofibrils can be prepared *in vitro*, delivered to cells and released from endosomes. I will discuss, how super-resolution microscopies from CLEM to STED could attain high enough resolution to "see" where the oligomers reside. Do they interact with mitochondrial and/ or other organelle membranes, do they produce increased ROS and lower cell viability? Down-stream processes of an amyloid pore formation could then be determined by Western blots and proteomics. I also will discuss literature data along these lines.

USE OF HNRNP PROTEINS AS MODIFIERS OF TDP-43 FUNCTIONS IN ALS AND FTLD NEUROPATHOLOGICAL PATHWAYS

Sara Cappelli, Maurizio Romano, Francesca Paron, Urša Šušnjar, Cristiana Stuani, Emanuele Buratti
ICGEB, Trieste, Italy
buratti@icgeb.org

Aims: Heterogeneous ribonuclear proteins (hnRNPs) are an abundant class of nuclear factors that have the function of binding nascent RNA molecules as soon as they are transcribed and have been recently described to play an important role in neurodegenerative diseases. In particular, ALS is a disease in which RNA binding proteins belonging to the hnRNP family (such as TDP-43 and FUS) and RNA-repeat expansions (C9orf72) have been shown to play a major role in its onset and progression. These discoveries have greatly expandend our knowledge of the basic mechanisms that may become altered and lead to disease. However, at the same time, all this complexity has made it extremely difficult to understand exactly which RNA alterations are directly connected to neuronal death.

Methods and Results: Using combined *in vivo* ALS models and RNAseq analysis of human neuronal cell lines we have previously shown that evolutionary conserved hnRNPs present in *Drosophila melanogaster* can robustly affect TDP-43 toxicity, especially in gain-of-function disease models (Appocher et al., 2017, NAR). Unfortunately, these identified factors do not represent ideal "druggable" targets, because each of them plays many important roles within cells. Altering their general expression to rescue/slow-down TDP-43 toxicity will therefore not be very feasible *in vivo*, as both their overexpression/downregulation is likely to be toxic.

Conclusions: For this reason, we are currently using a more refined approach of combining transcriptomic analyses to identify commonly regulated transcripts by these hnRNP factors and use these more specific targets to rescue the consequences of TDP-43 misregulation.

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Molecular basis of neurodegeneration

Organizers: Boris Rogelj (Ljubljana, SI) and Tibor Hortobagyi (Szeged, HU)

PATHOLOGY AND CURRENT MOLECULAR CLASSIFICATION OF ALS/FTD

Tibor Hortobágyi[1,2,3,4]

1Institute of Pathology, Faculty of Medicine, University of Szeged, Szeged, Hungary;
2MTA-DE Cerebrovascular and Neurodegenerative Research Group, University of Debrecen, Debrecen, Hungary;
3Department of Old Age Psychiatry, Institute of Psychiatry Psychology & Neuroscience, King's College London, London, UK;
4Centre for Age-Related Medicine, SESAM, Stavanger University Hospital, Stavanger, Norway

tibor.hortobagyi@kcl.ac.uk

Amyotrophic lateral sclerosis (ALS) is the major motor neurone disorder. The hallmark features are progressive, irreversible motor neuron loss leading to denervation atrophy of muscles and death usually within 5 years of disease onset. The hallmark proteins of the pathognomonic inclusions are either SOD-1, TDP-43 or FUS; rarely the disease is caused by mutation of the respective genes. Frontotemporal lobar degenerations (FTLDs) are genetically, neuropathologically and clinically heterogeneous dementias presenting with three major clinical syndromes dominated by behavioural, language and motor disorders, respectively. The characteristic aggregate-forming proteins in non-tau FTLDs are TDP-43 and FUS. It has been known for long that frontotemporal dementia (or less severe forms of cognitive impairment) may coexist with ALS. Recent discoveries in genetics (e.g. *C9orf72* mutation) and the subsequent neuropathological characterisation have revealed remarkable overlap between ALS and non-tau FTLDs also on molecular level indicating common molecular pathways in pathogenesis. After an historical overview we demonstrate and compare the macroscopic and microscopic appearances and molecular characteristics with emphasis on genetic background, neuroanatomical distribution and morphology of abnormal protein aggregates (and their possible association with specific mutations). The clinico-pathological classifications and correlations are also discussed.

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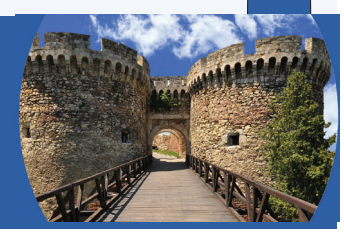

Friday, July 12, 2019

8:30–10:10

Room Atlantic 2

Symposium 18

Modelling of Neuronal disorders through cell reprogramming

Organizers: Marija Mihailovic (Milan, IT) and Milena Stevanovic (Belgrade, RS)

DE HUMANI CORPORIS FABRICA: ORGANOID-BASED DECONVOLUTION OF NEUROPSYCHIATRIC DISORDERS AT SINGLE CELL RESOLUTION

Giuseppe Testa
University of Milan, Milan, Italy
giuseppe.testa@unimi.it

Our work focuses on a particularly informative set of neurodevelopmental disorders caused by point mutations or dosage imbalances in chromatin regulators that operate in inter-related pathways. Across these conditions, we start from densely phenotyped clinical cohorts and integrate multi-layered omics, single cell dynamics and high-end computing into a disease modelling pipeline that combines human stem cell and 3D brain organoid-based approaches with the murine experimental system to achieve mechanistic dissection across the transcriptomic, epigenomic, proteomic and functional layer. Here I discuss the latest insights from our work on the single-cell level deconvolution of dosage-dependent alterations in developmental pathways in the context of the first comprehensive meta-analysis of omic profiles from brain organoids datasets, defining a matrix of standards and criteria to inform neurodevelopmental disease modelling studies and highlighting the value of cross-disorders analyses for the elucidation of convergent pathogenic hubs.

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REVERSE ENGINEERING THE BRAIN TO UNDERSTAND NEURODEVELOPMENTAL DISORDERS

Nael Nadif Kasri

Department of Human Genetics, Radboudumc, Donders Institute for Brain, Cognition, and Behaviour, Nijmegen, The Netherlands

n.nadif@donders.ru.nl

Neurodevelopmental disorders (NDDs), including intellectual disability (ID) and autism spectrum disorder (ASD), are genetically and phenotypically heterogeneous. Despite the identification of Mendelian mutations in hundreds of genes that give rise to some type of NDD, our understanding of the key molecular players and mechanisms is still fragmented.

The recent developments in induced pluripotent stem cells (iPSCs) have provided us with the ability to model patient specific neuronal networks. We studied the development of neuronal networks of iNeurons derived from patients with ID and epilepsy. To this end we monitored the electrophysiological activity of neuronal networks coupled to multi-electrode arrays (MEAs) over time and compared their activity to healthy controls and between syndromes. We identified robust neuronal network parameters across independent healthy controls and have identified disease-specific network phenotypes. Our data indicate that neuronal network measurements of iNeurons on MEAs is a robust and sensitive method to perform genotype-phenotype analyses for NDDs and can be a powerful platform for drug screening assays.

ASTROCYTE-BASED CELL THERAPY: NEW HOPE FOR AMYOTROPHIC LATERAL SCLEROSIS PATIENTS?

Izrael Michal, Slutsky Shalom Guy, Hasson Arik, Krush Paker Lena, Kuperstein Graciela, Shiran Yehezkel Ionescu, Ella Volman, Chebath Judith and Revel Michel.

R&D and Neurodegenerative diseases at Kadimastem Ltd., Weizmann Science Park, Nes-Ziona, Israel

a.hasson@kadimastem.com

Background: ALS is a Motor Neuron (MN) disease characterized by the loss of MNs in the central nervous systems. As MNs die, patients progressively lose their ability to control voluntary movements, become paralyzed and eventually die from respiratory/ deglutition failure. Despite the selective MN death in Amyotrophic lateral sclerosis (ALS), there is growing evidence that malfunctional astrocytes play a crucial role in disease progression. Thus, transplantation of healthy astrocytes may compensate for the diseased astrocytes.

Methods: we developed a GMP-grade protocol for generation of astrocytes from human embryonic stem cells (hESC) that is involved with derivation of astrocyte progenitor cells (APC) from hESCs. These APC can be expanded in large quantities and stored frozen as cell banks. Further differentiation of the APC yields an enriched population of astrocytes (AstroRx). AstroRx cells were injected intrathecally to hSOD1^{G93A} transgenic mice and rats to evaluate their therapeutic potential. The safety and biodistribution of AstroRx were evaluated in a nine-month study conducted in immunodeficient NSG mice under good laboratory practice (GLP) conditions.

Results: *In vitro*, AstroRx possess the activities of functional healthy astrocytes, including glutamate uptake, promotion of axon outgrowth and protection of MNs from oxidative stress. A secretome analysis shows that these AstroRx also secrete several inhibitors of metalloproteases as well as variety of neuroprotective factors (e.g. TIMP-1&2, OPN, MIF and Midkine). Intrathecal injections of the AstroRx to transgenic hSOD1^{G93A} mice and rats significantly delayed disease onset and improved motor performance compared to sham-injected animals. Safety study in immunodeficient mice showed that intrathecal transplantation of AstroRx is safe. Transplanted AstroRx attached to the meninges along the neuroaxis and survived for the entire duration of the study without formation of tumors or teratomas.

Conclusion: our findings demonstrate the safety and potential therapeutic beneficiary of intrathecal injection AstroRx for the treatment of ALS.

Clinical Trial: A phase I/IIa clinical trial (clinical.gov identifier: NCT03482050) to evaluate the safety and efficacy of AstroRx cells in ALS patients is currently ongoing in Hadassah medical center, Jerusalem, Israel. A first cohort of five patients were already intrathecally injected with 100 million of AstroRx. At that concentration of cells, the treatment was found as tolerable and safe. Interim look of this cohort is expected by fall of 2019 while the experiment is progressing to cohort B, where patients will be injected intrathecally with 250 million of AstroRx cells.

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SYMPOSIUM 18

MODELLING OF NEURONAL DISORDERS THROUGH CELL REPROGRAMMING

Organizers: Marija Mihailovic (Milan, IT) and Milena Stevanovic (Belgrade, RS)

DECONVOLUTION OF GENE REGULATORY NETWORKS DOWNSTREAM OF 7Q11.23 DOSAGE IMBALANCES IN WILLIAMS-BEUREN SYNDROME (WBS) AND 7Q11.23 MICRODUPLICATION SYNDROMES (7DUP)

Mihailovich M[1,2]., Germain PL[1]., Shyti R[1]., Pozzi D.[3], D'Agostino G.[1], Troglio F.[1], Noberini R.[1], Liu Y.[4], Aebersold R.[4], Bonaldi T.[1] and Giuseppe Testa[1,2]

1European Institute of Oncology, Milan, Italy;
2Department of Oncology and Hemato-Oncology, University of Milan, Italy;
3Humanitas University, Milan, Italy;
4Institute of Molecular Systems Biology, ETH Zurich, Switzerland

mihailovicm@gmail.com

An intriguing model to study molecular circuits regulating cognitive functions and intellectual disabilities are two neurodevelopmental disorders, Williams-Beuren syndrome (WBS) and 7q-microduplication syndrome (7dupASD, 7dup) caused by symmetrical copy number variations (CNV) of 7q11.23. Deletion (WBS) or duplication (7dupASD) of 26-28 genes in WBS-critical region displays a striking combination of shared and symmetrically opposite phenotypes, including at the neuro-cognitive level. We analyzed iPSC and iPSC-derived induced glutamatergic neurons (iNeurons) generated from 3 WBS, 3 controls, 3 7dup patients, including the CRISPR- engineered full allelic series of 7q11.23 CNV in an isogenic setting. We profiled both, iPSC and iNeurons, at the level of transcriptome, translatome and proteome by RNAseq, RIBOseq and label-free quantitative proteomics, respectively. Our analysis uncovered symmetrical dynamics of neuronal maturation and intrinsic excitability between WBS and 7dup, that point towards an early neuronal maturation and lower intrinsic excitability in 7dup, opposed to delayed maturation and higher intrinsic excitability in WBS when compared to healthy neurons. In addition, we also observed an extensive downregulation of ribosomal proteins and their transcriptional regulator, LRP2, in 7dup. The link between 7q11.23 CNV, ribosomal proteins expression and altered neuronal function is currently under investigation.

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SYMPOSIUM 19

NEURONAL BASIS OF INNATE AND LEARNED BEHAVIOURS

Organizers: Sanja Mikulovic (Bonn, DE)

DISYNAPTIC INHIBITION PROMOTES SYNCHRONY BETWEEN STRIATAL CHOLINERGIC INTERNEURONS AND IS REGULATED BY DOPAMINE VIA D2 RECEPTORS

M. Dorst[1], A. Tokarska[1], M. Zhou[1], K. Lee[2], S. Stagkourakis[1], C. Broberger[1], S. Masmanidis[2], G. Silberberg[1].

1Karolinska Institutet - Stockholm (Sweden);

2University of California, Los Angeles, Los Angeles United States of America

gilad.silberberg@ki.se

Striatal activity is dynamically modulated by acetylcholine and dopamine, both of which are essential for proper basal ganglia function. Synchronized pauses in the activity of striatal cholinergic interneurons (ChINs) are correlated with elevated activity of midbrain dopaminergic neurons, whereas synchronous firing of ChINs induces local release of dopamine. The mechanisms underlying ChIN synchronization and its interplay with dopamine release are not fully understood. Here we show using multineuron patch-clamp recordings, voltammetry, optogenetics, chemogenetics, and in vivo recordings, that robust disynaptic inhibition between ChINs acts as an efficient synchronization mechanism. Inhibitory disynaptic responses were elicited by single action potentials in ChINs and showed a high degree of recurrence within the ChIN network. Disynaptic inhibition was attenuated by dopaminergic midbrain afferents acting on D2 receptors. Our results present a mechanism supporting synchronization of activity and pauses across the ChIN population and a novel form of interaction between striatal acetylcholine and dopamine.

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SYMPOSIUM 19

NEURONAL BASIS OF INNATE AND LEARNED BEHAVIOURS

Organizers: Sanja Mikulovic (Bonn, DE)

DYNAMICS OF PREFRONTAL CORTICAL NEURAL ENSEMBLES DURING FEEDING BEHAVIOURS IN FREELY BEHAVING MICE

A. Petzold, T. Korotkova

Max Planck Research Group "Neuronal circuits and behaviour", Max Planck Institute for Metabolism Research, Cologne, Germany/Institute of Vegetative Physiology, Medical Faculty, University of Cologne, Germany

anne.petzold@sf.mpg.de

Feeding is a complex phenomenon encompassing a sequence of different behaviours such as foraging, food detection, approach and evaluation, as well as consumption. While the drive to feed is innate, feeding-related behaviours are shaped by a composition of environmental and internal cues, as well as previous experience and individual preferences . The prefrontal cortex (PFC) has long been implicated in the regulation of feeding behaviours, particularly regarding the anticipation and evaluation of the rewarding properties of food, the current state of satiety, and the ensuing motivation to feed. We have recently shown that gamma-rhythmic activation of PFC projections to the lateral septum promotes food-seeking. However, it is not known whether the same or different PFC cell ensembles encode various stages of feeding-related behaviours, whether activity of PFC cells depends on metabolic state of an animal and how it reflects changes in environmental cues. To address these questions, we investigate the dynamics of neural ensemble activity of the PFC throughout the stages of feeding under different environmental and internal constraints such as varying levels of food availability and satiety. For this purpose, we perform calcium imaging of large populations of PFC excitatory neurons using a miniaturized microscope in the freely moving mouse during spontaneous exploration, foraging, and feeding. Recordings of the same cells across multiple days and behavioural paradigms enable the identification of the cortical neural ensembles that encode various components of such innate behaviours. The concomitant optogenetic perturbation of excitatory ensembles of the PFC allows us to evaluate the functional relevance of PFC neural ensembles in shaping feeding behaviour under varying conditions. Through this approach, we dissect the contribution of PFC ensemble dynamics to the ongoing adaptation of feeding behaviour in the face of the constantly changing external and internal environment.

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Symposium 19

Neuronal basis of innate and learned behaviours

Organizers: Sanja Mikulovic (Bonn, DE)

THE ROLE OF ACTIVE BEHAVIOUR IN SHAPING VISUAL PROCESSING

Janelle M.P. Pakan[1,2,3]

1Center for Behavioral Brain Sciences, Magdeburg, Germany;
2Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke University, Magdeburg, Germany;
3German Center for Neurodegenerative Diseases, Magdeburg, Germany

janelle.pakan@med.ovgu.de

One may assume that neuronal encoding in sensory brain regions would provide a stable and robust representation of the external world; however, a growing body of research has found that even in early visual processing centres neuronal responses to visual stimuli are modulated by arousal and motor activity and are highly shaped by experience, even into adulthood. Here, we use two-photon imaging in headfixed behaving mice to examine the impact of visual, reward, and self-motion-related inputs to encode behaviorally-relevant stimuli and spatial locations, and further to determine the influence of active learning on stimulus representation in primary visual cortex (V1). We found that a population of V1 neurons encode behaviorally-relevant spatial locations, based on either visual cues or on self-motion feedback when visual cues are absent. Additionally, active task-engagement in a VR environment, where visuomotor feedback was congruent, increased the proportion of neurons that were responsive to a repeatedly presented visual stimulus. Conversely, during passive viewing habituation was observed to the same repeatedly presented stimulus. These alterations in primary visual processing by active behaviours may be critical to increase the salience of behaviourally-relevant stimuli in the environment and for successful visually guided navigation.

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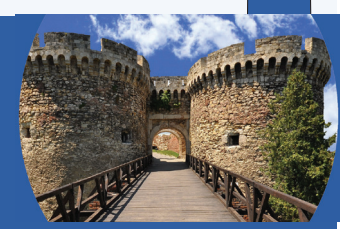

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NEURONAL BASIS OF INNATE AND LEARNED BEHAVIOURS

Organizers: Sanja Mikulovic (Bonn, DE)

ON MOTION AND EMOTION – NEURONAL CIRCUITS UNDERLYING LOCOMOTION AND AVERSIVE BEHAVIOR IN THE HIPPOCAMPUS/MEDIAL SEPTUM SYSTEM

Sanja Mikulovic

DZNE Bonn, Bonn, Germany

sanja.mikulovic@dzne.de

Aims: Hippocampus and medial septum play a pivotal role in movement control and emotional information processing. Theta oscillation (4-12 Hz) is one of the most prominent rhythms of the brain. Emerging research evidence points to the existence of several theta subtypes related to movement, cognition and emotion. Theta frequency has been shown to predict the intensity of subsequent locomotion, but also the processing of emotion-related stimuli. However, little is known about neuronal circuits underlying different types of theta rhythms. We here present the role of oriens-lacunosum/moleculare expressing Chrna2 receptor ($OLM^{\alpha 2}$) interneurons in regulating specific type of theta activity and control innate anxiety responses to predator odor. Furthermore, we present the role of different excitatory and inhibitory cell types involved in motor execution versus aversion-related oscillatory activity.

Methods: We used a combination of optogenetics and local field potential (LFP) recordings to study the role of OLM interneurons in regulating theta activity and predator odor innate anxiety behavior. We furthermore use 2 Photon Calcium imaging, in combination with electrophysiology, in a spatial reward learning task. We are investigating how different cell types contribute to processing of different stimuli and underlying oscillatory patterns.

Results: We show that ventral hippocampus OLM cell stimulation *in vivo* generates cholinergic-dependent type 2 theta oscillations in both anesthetized and freely behaving mice. We further show that type 2 theta can coexist with movement-driven type 1 theta activity. Theta oscillations induced by $OLM^{\alpha 2}$ cell stimulation were directly related to a considerable increase in risk-taking behavior in a predatory odor innate anxiety test. We further show the involvement of different cell types in processing of motor-execution and aversive stimuli in the hippocampus. Finally, we are investigating the role of the medial septum input on hippocampal cellular coding and the projection patterns of the imaged cell types to the associated regions.

Conclusion: We propose that different, and in some cases overlapping, neuronal networks underly different oscillatory subtypes associated to locomotion in presence or absence of aversive stimuli.

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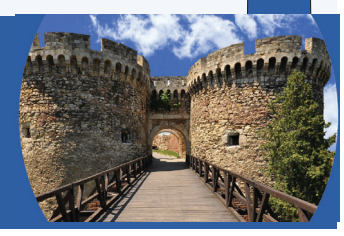

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NEURONAL BASIS OF INNATE AND LEARNED BEHAVIOURS

Organizers: Sanja Mikulovic (Bonn, DE)

COMBINED EXPERIMENTAL AND COMPUTATIONAL STRATEGIES FOR CONSTRAINING NEURONAL FUNCTION OF O-LM HIPPOCAMPAL INTERNEURONS IN MNEMONIC BEHAVIOURS

Vladislav Sekulic

Laboratory for Circuit and Behavioral Physiology, RIKEN; Center for Brain Science, Saitama, Japan

vlad.sekulic@gmail.com

Aims. The oriens-lacunosum/moleculare (O-LM) cell is a class of inhibitory interneuron found in the hippocampus. O-LM cells are active during theta rhythmic activity, a marker of the hippocampal "on" state. Due to conflicting reports in the literature, the contribution of O-LM cells to theta activity is unclear. We present research into computational properties of O-LM cells that sheds light on the ways in which they may contribute to hippocampal function.

Methods. In vitro electrophysiological recordings and immunohistochemical labelling of identified O-LM cells in SOM-Rosa-Cre mice have been combined with multi-compartment modelling to capture single cell electrophysiological phenotypes of O-LM cells.

Results. We examined the activity of experimentally-constrained, biophysically realistic computational models of O-LM cells during in vivo-like oscillatory states. We found that O-LM cells likely do not pace local hippocampal theta rhythms, as some studies previously suggested, but are tuned to participate during theta activity. We further found, through electrophysiological recordings and morphological reconstructions of O-LM cells, that O-LM cells express hyperpolarization-activated, mixed cation channels (h-channels) in their dendrites, which was subsequently confirmed using fluorescence immunohistochemistry. Simulations indicated that h-channels expressed in dendrites may allow O-LM cells to participate in a range of theta states, including changes in theta rhythms during, for instance, running activity in rodents.

Conclusions. We propose that the expression of dendritic h-channels endows O-LM cells with a robust ability to maintain their theta activity across network states. Our work further demonstrates the utility of combining computational and experimental approaches for elucidating neuronal function in behaving animals.

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SYMPOSIUM 20

COMPUTATIONAL AND SYSTEMS BIOLOGY IN NEUROLOGICAL DISORDERS

Organizers: Isil Kurnaz (Gebze / Kocaeli, TR)

UNDERSTANDING UPPER MOTOR NEURON BIOLOGY VIA OMICS DATA FROM GENES AND PROTEINS

Hande Ozdinler

Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

ozdinler@northwestern.edu

Upper motor neurons are located in layer 5 of the motor cortex and they play a unique role for the initiation and the modulation of movement. Their ability to collect, integrate, translate and transmit cerebral cortex's input to spinal cord targets is responsible for our motor function. Therefore, their degeneration leads to neurodegenerative diseases that are characterized by motor function defects, paralysis, and eventual death. Understanding the molecular and cellular basis of their vulnerability and progressive degeneration is important for building effective treatment strategies especially for motor neuron diseases, such as primary lateral sclerosis, hereditary spastic paraplegia and amyotrophic lateral sclerosis. Since cerebral cortex is very complex and heterogenous, investigation of one neuron type is challenging. Therefore, we initially generated a reporter line in which the upper motor neurons are genetically labeled with eGFP expression that is stable and long-lasting, then we crossed this reporter line to well-defined and characterized mouse models of motor neuron diseases that display progressive upper motor neuron loss. Since upper motor neurons are labeled with fluorescence, they can be visualized *in vivo*. Most importantly they are purified using fluorescence activated cell sorting (FACS) mediated approaches at different ages and stages of disease initiation so that upper motor neurons that display selective vulnerability among many other cortical neurons and cells can be isolated as a pure neuron population. The distribution of mRNA within these neurons as well as the presence of key proteins can then be investigated by RNASeq and proteomics analyses. We have studied the dynamic changes in gene expression profiles of upper motor neurons that become diseased due to mSOD1 expression, TDP-43 pathology and lack of alsin function. Our ongoing studies begin to reveal the secrets of their selective vulnerability as well as the common and unique cellular events that are responsible for their degeneration. Here, we will discuss our recent findings and how this information can be utilized for building effective treatment strategies for motor neuron diseases.

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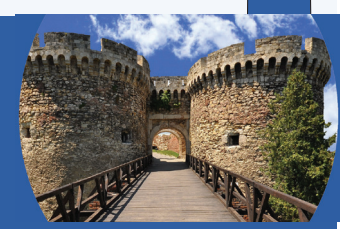

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COMPUTATIONAL AND SYSTEMS BIOLOGY IN NEUROLOGICAL DISORDERS

Organizers: Isil Kurnaz (Gebze / Kocaeli, TR)

ELUCIDATION OF PARKINSON'S DISEASE MECHANISMS BY MAPPING TRANSCRIPTOME DATA ON MOLECULAR INTERACTION NETWORKS

Tunahan Çakır

Gebze Technical University, Department of Bioengineering, Gebze, Kocaeli, Turkey

tcakir@gtu.edu.tr

Integrative analysis of genome-wide data with molecular interaction networks has high potential to reveal molecular mechanisms of diseases and predict candidate drug targets. We used several bioinformatics approaches to map transcriptome data from Parkinson's Disease on a brain-specific genome-scale metabolic network and protein-protein interaction network. The transcriptome data used in this study came from public databases for post-mortem tissues and from our in vitro 6-OHDA Parkinson's Disease model. Since metabolism supplies required chemicals for several vital cellular processes via a number of biochemical reactions, the network of these reactions were taken into account in our simulations, leading to predictive computational models on glucose and oxygen consumption rates and lactate production rates for the disease-affected cells. The partial dysfunction of mitochondria was also predicted. Additional use of protein-protein interaction networks, which has a focus on signaling pathways, enabled a more thorough investigation of the disease molecular mechanisms. Among thousands of interactions, groups of interacting proteins were discovered that showed significant changes in the disease. The computational algorithms were also applied to both network types to predict a number of candidate drug targets, which were analyzed via the repositioning of available drugs. The utilized systems biology approach enabled a molecular documentation of the disease from both metabolic and signaling aspects.

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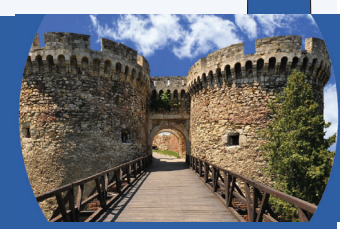

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COMPUTATIONAL AND SYSTEMS BIOLOGY IN NEUROLOGICAL DISORDERS

Organizers: Isil Kurnaz (Gebze / Kocaeli, TR)

SYSTEMS BIOMARKERS FOR ACCURATE DIAGNOSIS, PROGNOSIS AND THERAPY IN NEUROLOGICAL DISORDERS

Kazım Yalçın Arga

Department of Bioengineering, Marmara University, Istanbul, Turkey

kazim.arga@marmara.edu.tr

Identification of efficacious biomarkers is crucial for accurate diagnosis and prognosis of diseases as well as the development of efficacious treatment strategies. However, it is a challenging task to develop highly accurate and robust biomarkers due to the complexity of the molecular biology behind the pathologies. Traditionally, biomarker discovery was focused on identification of molecular biomarkers by comparing the expression levels in different phenotypes. This reductionist point of view has not been very successful since the development and progression of the disease is mostly caused from the interplay of a group of correlated molecules rather than from the malfunction of the individual gene or gene product. It is believed that dynamic alternations of complex interaction networks and molecular sub-networks can represent and influence responses of cells or organs to real-time changed microenvironment. The utilization of functional genomics datasets and biomolecular networks, which provide a global view of the complex biological systems via describing the functional relationships among molecules enabled more complicated biomarker definitions, and inspired us with hope to develop highly accurate and robust biomarkers for accurate diagnosis, prognosis and prevention of complex human diseases, including neurological disorders. As an innovative concept, systems biomarkers (a set of biomarkers and their dynamic interactions) was proposed as a new type of biomarkers. The present study highlights the concept of systems biomarkers with special focus on neurological diseases, and summarizes current methodologies to determine system biomarkers with an emphasis on our differential co-expression and differential interactome approaches.

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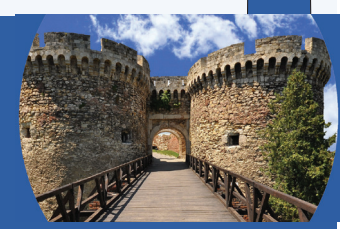

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COMPUTATIONAL AND SYSTEMS BIOLOGY IN NEUROLOGICAL DISORDERS

Organizers: Isil Kurnaz (Gebze / Kocaeli, TR)

COMPUTATIONAL BIOLOGY FOR STUDYING NEURODEVELOPMENTAL DISORDERS AND TUMOR FORMATION

Isil Kurnaz[1,2], Yigit Koray Babal[1,2], Basak Kandemir[2]

1Gebze Technical University, Dept Molecular Biology and Genetics, Gebze-Kocaeli, Turkey;
2Gebze Technical University, Institute of Biotechnology, Gebze-Kocaeli, Turkey

isil.kurnaz@gmail.com

Aims: The brain is a complex organ with over 100 billion neurons and nearly 10 to 50 times more glial cells, and more than ten thousand genes expressed in each region. The molecular activity of the developing and adult brain is divergent in various brain regions, both spatially and temporally, reflecting its plasticity. Understanding the brain at the molecular level is essential for a comprehensive understanding of how the brain normally Works, as well as what goes wrong in many developmental problems or diseases. Transcriptomic, proteomic and metabolomic approaches have been extensively used to understand the underlying mechanisms of many neurodegenerative diseases such as Alzheimer's, Parkinson's or ALS, as well as brain tumorigenesis.

Methods: In this talk, we will give a brief overview of existing literature on multiomic studies related to biomarker identification and / or drug discovery, and focus on our transcriptomic approaches to the effect of Elk-1 transcription factor on neuronal survival as well as brain tumor proliferation. Q-PCR validation, *in silico* promoter analysis, and whole cell kinetic modeling approaches will also be presented.

Results: We have carried out microarray analysis in neuroblastoma cells overexpressing exogenous Elk1-VP16 protein under normoxic and hypoxic conditions, and validated the results using qPCR analysis. After *in silico* analysis of transcription factor binding sites on putative target promoters, potential Elk-1 binding *ets* motifs have been confirmed in chromatin IP analysis. Target pathways of Elk-1 transcription factor include not only common culprits of various neurodegenerative disorders including APP, presenilin, BACE etc, but also various nervous system development or early embryonic development pathway elements. We have also deterrmined many ETS domain superfamily members regulated by Elk-1 overexpression, and have generated a computational model for cross-regulation of ETS family members, and will discuss how this interconnectivity may be crucial for early development events.

Conclusions: Both nervous system development and brain tumorrigenesis are complex diseases involving multiple biological interactions, which represents a challenge in understanding the underlying mechanisms. High-throughput experimental findings are quite helpful in generating insight and information that can be used in *in silico* models, which in turn can be used to predict dynamic behavior of systems that can further be tested and validated in experimental setups. Here we presented how transcriptome data can lead to a novel understanding of transcriptional interplay among ETS proteins, which in turn can be used to predict proliferation, differentiation or tumorigenesis outcome with respect to cellular homeostasis in the future.

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Room Pacific

SYMPOSIUM 21

CURRENT ADVANCES IN UNDERSTANDING SYNAPTIC FUNCTION AND DYSFUNCTION

Organizers: Peter Penzes (Chicago, IL, USA)

CHARTING THE MOLECULAR LANDSCAPE OF DIVERSE SYNAPSES *IN VIVO*

Scott H. Soderling

Department of Cell Biology, Duke University, Durham, North Carolina, USA

scott.soderling@duke.edu

Over the past three decades, purification and analysis of protein complexes at the mature excitatory postsynapse has led to fundamental insights in neurobiology. These insights include how receptor trafficking, synaptic adhesion, cytoskeletal remodeling, and protein phosphorylation contribute to the synaptic plasticity underlying learning and memory. Moreover, genetic perturbations of excitatory postsynaptic proteins are now known to contribute to developmental brain disorders and psychiatric conditions.-In contrast to the well-studied excitatory synapse, biochemical purification and analysis of other neuronal structures, such as immature synapses or the inhibitory postsynaptic specialization, has remained largely intractable. We have developed a chemico-genetic proteomic approach to resolve the molecular composition of diverse synapses as they exist *in vivo*. Results from several previously unexplored proteomes and the analysis of several novel synaptic proteins will be discussed, including the implications of how these proteins may contribute to multiple brain disorders.

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SYMPOSIUM 21

CURRENT ADVANCES IN UNDERSTANDING SYNAPTIC FUNCTION AND DYSFUNCTION

Organizers: Peter Penzes (Chicago, IL, USA)

MECHANISM OF CA^{2+}-DEPENDENT REGULATION OF POSTSYNAPTIC BINDING CAPACITY

Yasunori Hayashi

Kyoto University Graduate School of Medicine, Kyoto, Japan

yhayashi-tky@umin.ac.jp

Neuronal circuits store information through the mechanism of synaptic plasticity, a process where synaptic transmission is strengthened or weakened. Long-term potentiation (LTP) is a major form of synaptic plasticity. A number of studies focused on the induction mechanism that triggers the delivery of AMPAR to the synapse surface. But not many studies elucidate the mechanism which retain the increased amount of AMPAR after it is delivered to the synapse. We hypothesized that CaMKII serves this role by interacting various postsynaptic proteins though unique T-site, which is usually masked by autoinhibitory domain. Activation of CaMKII by Ca2+/calmodulin opens up this site and allows binding of various proteins. NMDAR subunit NR2B is a prototypical protein that associate this site. But it shares only small proportion of synaptic proteins compared with CaMKII itself. By screening the proteins that binds this site, we isolated number of PSD proteins interact with CaMKII in this way. Notably, AMPAR binding proteins were among the isolated protein. Through this interaction, we propose that CaMKII serves as postsynaptic crosslinker which gathers and stabilizes various synaptic proteins though its dodecameric structure. This also reasonably explains the abundance of CaMKII at the synapse.

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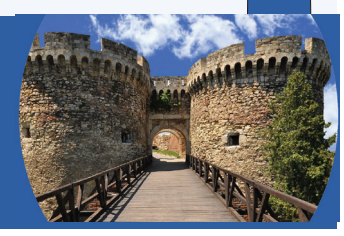

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SYMPOSIUM 21

CURRENT ADVANCES IN UNDERSTANDING SYNAPTIC FUNCTION AND DYSFUNCTION

Organizers: Peter Penzes (Chicago, IL, USA)

DIRECT QUANTITATIVE PROTEOMICS OF FUNCTIONALLY CHARACTERIZED GLUTAMATERGIC SYNAPSES

Noemi Holderith, Viktor Kis, Zoltan Nusser

Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary

noemi.holderith@koki.mta.hu

Cortical glutamatergic synapses display large structural, molecular and functional heterogeneity. Our knowledge regarding the relationship between their molecular and functional parameters is still fragmented and mostly derived from indirect correlation analysis. This is mainly due to methodological limitations that hindered the interrogation of the very same functionally characterized synapse at molecular level. Here I report the development of a highly sensitive method based on array tomography that allows the quantitative localization of many pre- and postsynaptic key molecules to individual synapses that have been previously functionally characterized using paired recording and multiple probability fluctuation analyses, 2-photon Ca^{2+} imaging or glutamate imaging.

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SYMPOSIUM 21

CURRENT ADVANCES IN UNDERSTANDING SYNAPTIC FUNCTION AND DYSFUNCTION

Organizers: Peter Penzes (Chicago, IL, USA)

PROTEOMIC PROFILING OF THE 16P11.2 MICRODUPLICATION MOUSE MODEL REVEALS ALTERATIONS IN ION CHANNEL TRAFFICKING

Forrest MP[1], Wang YZ[2], Piguel NH[1], Simkin D[2,3], Dionisio LE[1], Hawkins NA[3], Bagchi V[1], Dos Santos M[1], George AL Jr.[3,4], Kearney JA[3], Savas JN[2], Penzes P[1,4]

1Department of Physiology, 2Department of Neurology, 3Department of Pharmacology, 4Center for Autism and Neurodevelopment, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

p-penzes@northwestern.edu

Neuropsychiatric disorders have a complex genetic architecture consisting of common and rare risk variants. Rare genetic risk factors such as copy number variants (CNVs) are highly penetrant, and offer an opportunity to understand disease mechanisms which lead to common neuropsychiatric disorders. However, CNVs typically contain a large number of genes, and are associated with wide variety of clinical phenotypes, making the interpretation of CNVbased disease mechanisms a major challenge. Here, we studied the 16p11.2 microduplication, a rare CNV that confers risk of multiple neuropsychiatric conditions including schizophrenia, autism spectrum disorder, intellectual disability, bipolar disorder and Rolandic epilepsy. The 16p11.2 chromosomal region contains 27 protein-coding genes, but how these genes interplay to dysregulate brain function is currently unknown. We used unbiased quantitative proteomic profiling to uncover novel disease-relevant pathways in the 16p11.2 microduplication mouse model (dp/+), and used this as a basis to reveal unexpected cellular and behavioral phenotypes. We found an upregulation of ion channels and epilepsy risk factors identified through quantitative proteomic screening, which indicates that the 16p11.2 microduplication causes a widespread proteomic dysregulation in the mouse cortex, which converges on an upregulation of ion channels and epilepsy risk factors. Cortical pyramidal neurons from dp/+ mice are hyperexcitable, with a reduced threshold for action potential generation and an increase in spiking frequency after current injection. Neuronal networks from cortical cultures in vitro appear to be highly synchronized, with a lower overall activity. Consistent with this, the dp/+ mouse model is more susceptible to kainate-induced seizures. Finally our data suggest that the epilepsy risk gene PRRT2 (within the duplication region) may alter a subset of proteins involved in ion transport, which are disrupted in the dp/+ mouse model. Based on this experimental and previously published clinical evidence, we propose that a potential 'driver gene' within the duplicated region may be responsible for the phenotypes we describe. Our working model is that subsets of genes within the CNV impact specific cellular endophentypes, and together these converge to increase neuropsychiatric risk.

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Room Atlantic 1

SYMPOSIUM 22

SLEEP HOMEOSTASIS AND NEUROMODULATION – FROM LOCAL TO GLOBAL NEURONAL NETWORKS

Organizers: Jasna Saponjic (Belgrade, RS)

CHANGES IN SLEEP HOMEOSTASIS AND EEG SLOW-WAVES IN THE COURSE OF AGING IN MICE

Tom Deboer

Laboratory for Neurophysiology, Department of Cell and Chemical Biology, Leiden University Medical Center, Leiden, The Netherlands

t.de_boer@lumc.nl

As humans age the amount of sleep in general decreases and also the depth of sleep, as indicated by the amount of slow-wave activity (SWA, EEG power density below ~4 Hz) in NREM sleep, is also reduced. In rodents the opposite seems to be the case. Rats and mice sleep more in the course of aging. Long has been unclear whether and how EEG SWA in NREM sleep changes, but recent work from our laboratory and others has shown that SWA increases in the course of aging in mice. Neuronal activity of single cortical neurons during NREM sleep does not seem to change much and it is now thought that the increased SWA in mice is caused by a shift from global to more local connectivity in the cortex. In a follow up study we showed that the increase in SWA in the course of aging can be attenuated by providing the animals with a running wheel. This suggests that moderate voluntary exercise attenuates brain or cortical aging processes. In young animals voluntary running resulted in a redistribution of sleep and waking with more waking in the dark and less waking in the light period. This was the case even after the wheel had been removed for at least a week. The results show that in mice sleep in the course of aging may follow a different path compared to humans, but that the results of interventions to improve sleep can still be interpreted in a similar way.

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SLEEP HOMEOSTASIS AND NEUROMODULATION – FROM LOCAL TO GLOBAL NEURONAL NETWORKS

Organizers: Jasna Saponjic (Belgrade, RS)

CAN K-COMPLEXES FUNCTION AS SLEEP SENTINEL?

George Kostopoulos

University of Patras Medical School, Greece

gkkostop@upatras.gr

Aims: K-complexes (KCs) are prominent and widespread negative EEG waves characteristic of NREM-2 sleep and reflecting hyperpolarization of cortical neurons. Putative functions of KCs include a role of sentinel (Halasz, 2016) allowing safe sleep maintenance for bodily restorations and memory consolidation.

Methods: Whole night sleep studies using dense EEG (Kokkinos et al., 2013) and MEG tomography (Ioannides et al., 2009; 2017) traced the neurophysiological conditions of KC emergence, which allow us to investigate whether KCs can function as sentinel.

Results: KC fulfilled four criteria: (a) unconscious state prevailing immediately after sleep onset as marked by increased NREM background slow activity frontally and decreased fast posteriorly (b) sensitivity-responsiveness, as KC is a "reactive wave", preceded by a period of heightened responsiveness, while spectral power changes prior to KC emergence appear localized in mid-frontal brain areas involved in environmental monitoring. (c) capability for cognitive evaluation-decision taking, evidenced by the strong local gamma band activations in several midline cortical areas during NREM-2 and particularly theta and alpha band activations in the 2 seconds preceding KC in anterior cingulate cortex. KC must reflect a very dynamic system, since it blocks any coinciding spindles, while featuring a short burst of high theta-low alpha and brings the brain to a bistability state. (d) hypnagogic action, if stimulus does not constitute threat, since KC is a slow widely synchronizing wave, followed by spindles, and avoiding arousal by not allowing information to enrich consciousness.

Conclusions: The findings provide spatiotemporal constrains of KC emergence as a dynamic system, compatible with a sentinel role of KC and enabling further experimentation on this role.

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SYMPOSIUM 22

SLEEP HOMEOSTASIS AND NEUROMODULATION – FROM LOCAL TO GLOBAL NEURONAL NETWORKS

Organizers: Jasna Saponjic (Belgrade, RS)

NEURONAL NETWORK OF PARADOXICAL (REM) SLEEP AND ITS IMPLICATION IN LEARNING AND MEMORY AND SLEEP PATHOLOGIES

Luppi Pierre-Hervé

UMR 5292 CNRS/U1028 INSERM, Bron, France

luppi@sommeil.univ-lyon1.fr

Rapid eye movement (REM) sleep (also known as paradoxical sleep; PS) is characterized by EEG rhythmic activity resembling that of waking with a disappearance of muscle tone and the occurrence of REMs, in contrast to slow-wave sleep (SWS, also known as non-REM sleep) identified by the presence of delta waves. PH Luppi will report that the entrance from NREM to REM sleep is due to the intrinsic activation of REM-on hypothalamic MCH/GABAergic neurons. These neurons would inhibit during REM sleep a population of mesencephalic REM-off GABAergic neurons. This population of REM-off GABAergic neurons tonically inhibits during waking the glutamatergic neurons triggering the state of REM sleep localized in the pontine sublaterodorsal tegmental nucleus (SLD). The exit from REM sleep would be induced by the inhibition of the REM-on GABAergic neurons by waking systems such as the pontine and medullary noradrenergic neurons and the hypothalamic hypocretin. In addition, PH Luppi will make hypotheses on the mechanisms responsible for two main sleep pathologies, REM sleep behavior disorder and narcolepsy. He will propose that RBD is due to a neurodegeneration of the REM-on glutamatergic neurons triggering the atonia of REM sleep and localized in the SLD or that of the GABA/glycinergic premotoneurons localized in the ventromedial reticular formation and responsible for tonic hyperpolarization of motoneurons during REM sleep. Finally, PH Luppi will present new data on the cortical activation during REM sleep showing that only a few limbic structures known to be implicated in learning and memory are activated during REM sleep.

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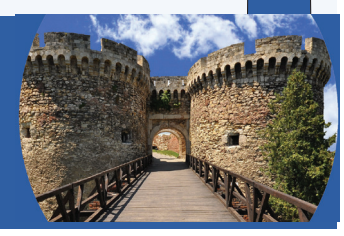

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SYMPOSIUM 22

SLEEP HOMEOSTASIS AND NEUROMODULATION – FROM LOCAL TO GLOBAL NEURONAL NETWORKS

Organizers: Jasna Saponjic (Belgrade, RS)

DISORDERS OF CORTICAL AND HIPPOCAMPAL SLEEP AND NREM/REM RELATED SLEEP SPINDLE DYNAMICS IN THE EXPERIMENTAL MODELS OF PARKINSON'S DISEASE

Jasna Saponjic

University of Belgrade, Department of Neurobiology, Institute for Biological Research - Sinisa Stankovic, Belgrade, Serbia

jasnasap@ibiss.bg.ac.rs

Sleep is a global phenomenon, orchestrated by specialized neuronal networks, but it is also a local phenomenon, or fundamental propriety of small neuronal groups. Sleep states are spatially non-uniform, or sleep and wakefulness might be simultaneously present in different brain regions. In the rat model of Parkinson's disease cholinopathy there is no change in sleep architecture, but the earliest functional biomarkers preceding "hypokinesia" are the topographically distinct and long-lasting sleep-related alterations in EEG oscillations at cortical and hippocampal levels, cortical drives and sleep spindles (SS). Moreover, two distinct REM states "emerge" in the motor cortex, with distinct cortical drives to dorsal nuchal muscles, and REM sleep "enriched" with sigma activity, with underlying alteration of SS dynamic and pattern, is the hallmark of earlier aging onset. In the hippocampus a sustainable increase of EEG delta vs. beta amplitude decrease during NREM sleep, along with an altered high voltage sleep spindle (HVS) dynamic during REM sleep preceded the "hypokinesia". In the hemiparkinsonian rat the long-lasting sleep fragmentation and augmented theta amplitude across all sleep states are followed by the increased SS density in the motor cortex and hippocampus during NREM sleep, but consistently shorter in the hippocampus. During REM sleep, the increased density of HVS in the motor cortex and the presence of consistently shorter HVS in the hippocampus lead to the increased theta and sigma synchronizations between them. Oscillatory rhythms in the EEG local field potentials underlie the basis of behavioral states and neurological diseases and their alterations are NREM/REM related.

Acknowledgement: This work was supported by Serbian Ministry of Education, Science and Technological Development Grant OI 173022.

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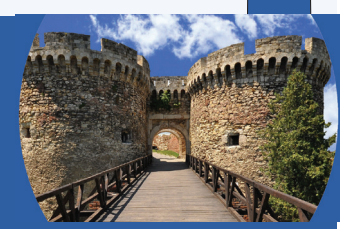

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SYMPOSIUM 23

NANOPARTICLES FOR THERAPY OF CNS DISEASES

Organizers: Aleksandra Isakovic (Belgrade, RS) and Vladimir Trajkovic (Belgrade, RS)

MULTI-BRANCHED GOLD NANOPARTICLES AS BRAIN-TARGETED NANO-VEHICLES FOR TREATMENT OF PARKINSON'S DISEASE

Alexandra Porter

Imperial College London, London, United Kingdom

a.porter@imperial.ac.uk

Clinical treatment strategies for Parkinson's disease (PD) only treat symptoms, without slowing down the disease progression, are short-acting, costly and often cause debilitating side effects. This shortcoming is because most drugs cannot efficiently reach neurons damaged in PD due to the relatively large size of drug molecules and highly impermeable blood-brain-barrier (BBB), which necessitates the use of higher dosages, often leading to severe side-effects. There is an urgent clinical requirement to devise small-size protective agents and strategies to deliver them to neurons, and very small (nano)-materials able to target and transport drugs across the BBB are opening up new treatment approaches. We have recently discovered small, easily producible synthetic peptides (H3 and H6 – based on S100A proteins that are upregulated in brain disorders) and demonstrated that they mimic the beneficial effects of the parent protein *in vivo* and in neuronal models of oxidative stress, excitotoxicity, and Parkinson's disease (PD)-related cytotoxicity, making them promising therapeutic candidates. However, these protectants cannot cross the BBB. I will present work in our group on development of functionalised "star"-shaped nanoparticles (nanostars) with a unique ability to cross the BBB *in vitro* in high quantities. We have also designed two types of H3/H6-conjugated nanocompounds, spherical and star-shaped gold nanostars (AuNP/AuNS) with the potential imaging capability in the NIR-II range and tested these compounds and their PEGylated versions for neurotrophic effect in cell models of neurodegeneration. I will present results that show the superior neuritogenic and neuroprotective efficiency of these H3/H6 nanostars over their spherical counterparts.

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SYMPOSIUM 23

NANOPARTICLES FOR THERAPY OF CNS DISEASES

Organizers: Aleksandra Isakovic (Belgrade, RS) and Vladimir Trajkovic (Belgrade, RS)

GRAPHENE-BASED NEURAL INTERFACES TO TARGET NETWORK EXCITABILITY

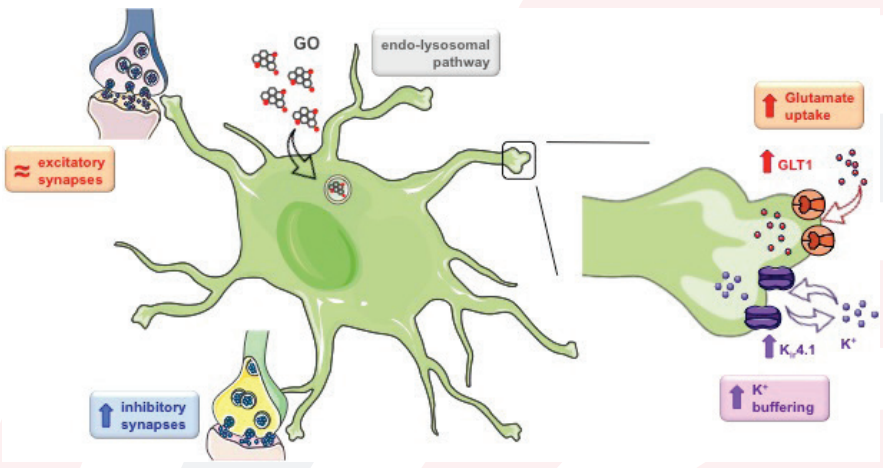
Mattia Bramini, Martina Chiacchiaretta, Anna Rocchi, Andrea Armirotti, Fabrizia Cesca, Fabio Benfenati

Center for Synaptic Neuroscience and Technologies, Istituto Italiano di Tecnologia, Genova, Italy

mattia.bramini@iit.it

The emerging interest toward applying graphene (G) and graphene-related materials (GRMs) for drug and gene delivery, biomedical imaging and diagnostic biosensors within the central nervous system (CNS) prompted neuroscientists to focus on the effects of the interaction of GRMs in contact with primary neural cells [1]. To fulfil this goal, it is mandatory to characterize the effects elicited by GRMs when in contact with the main neural cell populations, with the goal to evaluate their biocompatibility and accordingly any unwanted effects GRMs could potentially induce to living systems. In this scenario, we have focused on characterizing the G flake bio-interactions within the CNS, and the possibility of using both 2D and 3D G-based supports as biocompatible scaffolds for neurological applications. The aim is to exploit the conductive properties of graphene to modulate and control the activity of neural networks grown in strict contact with such structures. Our results show that although exposure to G materials does not impact neuronal and glial viability and network formation, it does nevertheless have important effects on neuronal and glial physiology [2,3,4]. We demonstrated that G oxide (GO) impact on several cellular processes including synaptic activity, intracellular Ca^{2+} dynamics and astrocyte glutamate uptake, thus on one side warranting caution when planning to employ this material for neurobiological applications, but on the other side suggesting GO could have protective effects in neuropathologies characterized by hyperexcitability.

We are conducting our research within the Graphene Flagship European project, WP4 (Health & Environment) and WP5 (Biomedical Technologies).



Schematic representation of the mechanisms of GO effects on primary astrocyte-neuron cocultures [3].

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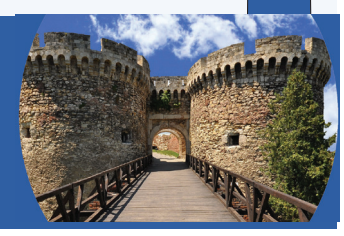

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Symposium 23

Nanoparticles for therapy of CNS diseases

Organizers: Aleksandra Isakovic (Belgrade, RS) and Vladimir Trajkovic (Belgrade, RS)

NANOPARTICLES FOR IN VIVO VISUALIZATION OF THE STEM CELLS AFTER TRANSPLANTATION IN THE MOUSE BRAIN USING MAGNETIC RESONANCE IMAGING

Marina Radmilovic Dobrivojevic[1], Igor M. Pongrac[1], Sinisa Skokic[1], Daniel Horak[2], Srecko Gajovic[1]

1University of Zagreb School of Medicine, Croatian Institute for Brain Research, Zagreb, Croatia;
2Institute of Macromolecular Chemistry, Academy of Sciences, Prague 6, Czech Republic

srecko.gajovic@hiim.hr

The design of the medical interventions using stem cells is dependent on the understanding of the fate and interactions of stem cells and the host brain. Magnetic resonance imaging of superparamagnetic iron oxide-labeled cells can be used as a non-invasive technique to track stem cells after transplantation. Iron oxide nanoparticles have properties allowing them to act as stem cell tracers, but they differ in cellular uptake and side effects. The aim of this study was to evaluate labeling efficiency of poly(L-lysine) and D-mannose-coated maghemite nanoparticles in neural stem cells (NSC), verify whether they could be visualized by MRI and test nanoparticles' biocompatibility. Custom-made maghemite nanoparticles were prepared and characterized and their cellular uptake, mechanism of internalization, cytotoxicity, viability and proliferation of neural stem cells were evaluated. Prussian blue staining revealed a concentration dependent intracellular uptake of iron oxide in neural stem cells. The methyl thiazolyl tetrazolium assay and calcein acetoxymethyl ester/propidium iodide assay demonstrated high labeling efficiency, viability and proliferation of neural stem cells. Cytochalasine D blocked cellular nanoparticle uptake indicating actin-dependent process, such as macropinocytosis to be the internalization mechanism for nanoparticles. Finally, immunocytochemistry analysis of neural stem cells after labeling showed that neural stem cells preserve their potential to differentiate. The labeled cells were visualized by ex vivo MRI and subsequently, their localization confirmed on histological sections.Although the progenitor properties and differentiation of the NSC were not affected by labeling, subtle effects on stem cells could be detected depending on dose increase, including changes in cell proliferation, viability, and neurosphere diameter. Improved biocompatibility and efficient cell labeling makes maghemite nanoparticles possible candidates for future neural stem cell in vivo tracking studies.

This study was co-financed by the Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience (project "Experimental and clinical research of hypoxic-ischemic damage in perinatal and adult brain"; GA KK01.1.1.01.0007 funded by the European Union through the European Regional Development Fund), and by the Croatian Science Foundation under the project IP-06-2016-1892 (RepairStroke). Multimodal imaging was done at Laboratory for Regenerative Neuroscience - GlowLab, University of Zagreb School of Medicine.

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SYMPOSIUM 23

NANOPARTICLES FOR THERAPY OF CNS DISEASES

Organizers: Aleksandra Isakovic (Belgrade, RS) and Vladimir Trajkovic (Belgrade, RS)

ANTI-NEUROINFLAMMATORY AND NEUROPROTECTIVE EFFECTS OF GRAPHENE QUANTUM DOTS

Ž. Stanojević[1], J. Tasić[1], S. Vidičević[1], S. Petričević[1], N. Tomonjić[1], Ćirić D[3], Martinović T[3], Kravić-Stevović T[3], Bumbaširević V[3], V. Trajković[2], A. J. Isaković[1]

1Institute of Medical and Clinical Biochemistry;
Faculty of Medicine;
University of Belgrade, Belgrade;
Serbia;
2Institute of Microbiology and Immunology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia;
3Institute of Histology and Embryology, Faculty of Medicine, University of Belgrade;
Belgrade;
Serbia,

zeljka.stanojevic@med.bg.ac.rs

Quantum dots (QDs) have enormous potentials for biomedical applications, owing to their unique photoluminescence properties, exceptional physicochemical properties, high photostability, biocompatibility and small size. Therefore, we aimed to investigated the therapeutic capacity of nano-sized graphene sheets, called graphene quantum dots (GQD), in experimental autoimmune encephalomyelitis (EAE), an animal model of immune-mediated central nervous system (CNS) damage. Intraperitoneally administered GQD (10mg/kg/day) accumulated in the lymph node and CNS cells of Dark Agouti rats in which EAE was induced by immunization with spinal cord homogenate in Complete Freund's adjuvant. GQD significantly reduced clinical signs of EAE when applied throughout the course of the disease (day 0-32), while the protection was less pronounced if the treatment was limited to the induction (day 0-7) post-immunization or effector (from day 8 onwards) phase of the disease. GQD treatment diminished immune infiltration, demyelination, axonal damage, and apoptotic death in the CNS of EAE animals. GQD also reduced the numbers of interferon-γ-expressing T helper (Th)1cells, as well as the expression of Th1 transcription factor t-bet and proinflammatory cytokines tumor necrosis factor, interleukin-1, and granulocyte-macrophage colony-stimulating factor in the lymph nodes and CNS immune infiltrates. The protective effect of GQD in EAE was associated with the activation of p38 and p42/44 mitogen-activated protein kinases (MAPK) and Akt in the lymph nodes and/or CNS. Collectively, these data demonstrate the ability of GQD to gain access to both immune and CNS cells during neuroinflammation, and to alleviate immune-mediated CNS damage by modulating MAPK/Akt signaling and encephalitogenic Th1 immune response.

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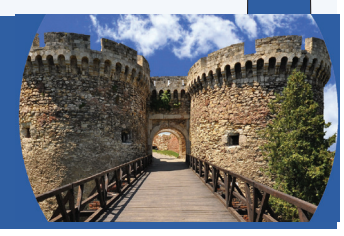

Friday, July 12, 2019

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Room Atlantic 2

SYMPOSIUM 23

NANOPARTICLES FOR THERAPY OF CNS DISEASES

Organizers: Aleksandra Isakovic (Belgrade, RS) and Vladimir Trajkovic (Belgrade, RS)

TARGETED DELIVERY TO THE BRAIN VIA TRANSPORT ACROSS THE BBB OF BIOLOGICS AND NANOPARTICLES CONJUGATED TO ANTI-TRANSFERRIN RECEPTOR ANTIBODIES

Torben Moos

Laboratory for Neurobiology, Biomedicine, Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

tmoos@hst.aau.dk

The ability to treat invalidating neurological diseases is impeded by the presence of the blood-brain barrier (BBB), which inhibits the transport of most blood-borne substances into the brain parenchyma. Targeting the transferrin receptor (TfR) on the surface of brain capillaries has been a popular strategy to give a preferential accumulation of biologically active drugs or nanomedicines, but several aspects of this targeting strategy remain elusive. I will report that TfR-targeted antibodies and gold nanoparticles (AuNPs) can accumulate in brain capillaries and further transport across the BBB to enter the brain parenchyma. A novel class of small single chain antibodies adapted from the shark immune system (a.k.a. vNAR antibodies) overcomes the obstacle of the BBB when targeted to brain capillary endothelial cells (BCECs) and accumulate in neurons. Concerning AuNPs, the uptake capacity is significantly modulated by the affinity and valency of the AuNP-conjugated antibodies. Specifically, antibodies with high and low affinities mediate a low and intermediate uptake of AuNPs into the brain, respectively, whereas a monovalent (bi-specific) antibody improves the uptake capacity remarkably. Our findings indicate that monovalent ligands may be beneficial for obtaining transcytosis of TfR-targeted nanomedicines across the BBB, which is relevant for future design of nanomedicines for brain drug delivery.

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Symposium 24

Mitochondrial mechanisms in neurodegeneration and neuromodulation in Parkinson's disease

Organizers: Vladimir S. Kostić (Belgrade, RS)

ROLE OF MITOCHONDRIA AND ENERGY METABOLISM IN MONOGENIC PD

Christine Klein

Institute of Neurogenetics, University of Luebeck, Luebeck, Germany

christine.klein@neuro.uni-luebeck.de

Recessively inherited Parkin and PINK1 mutations are the most prevalent causative genetic factor in early-onset PD (age of onset <40 years) accounting for up to 50% of familial cases and for about 10-20% of all early-onset cases. Interestingly, both proteins have been shown to function, at least in part, in the same pathway to remove damaged mitochondria by autophagy (mitophagy) and thereby maintaining integrity of the mitochondrial pool and energy metabolism. Parkin, located in the cytosol, is an E3 ubiquitin-protein ligase of the ubiquitin proteasome system that translocates to impaired mitochondria and targets outer mitochondrial membrane proteins for degradation by ubiquitination. PINK1 is a mitochondrial kinase that is also involved in mitochondrial homeostasis and required for efficient Complex I activity. Defects in Parkin and PINK1 result in an impaired electron transport chain, reduced ATP levels and defective mitochondrial morphology, as has been demonstrated in several cellular, drosophila, and also rodent models. Neurodegeneration in monogenic PD is also connected to changes in lipid homeostasis with inhibition of fatty acid synthase (FASN) suppressing toxicity induced by PINK1 deficiency in flies, mouse cells, and human endogenous cellular models. Lower FASN activity in PINK1 mutants decreases palmitate levels and increases the levels of cardiolipin, a mitochondrial inner membrane–specific lipid. Direct supplementation of cardiolipin to isolated mitochondria not only rescues the PINK1-induced complex I defects but also rescues the inefficient electron transfer between complex I and ubiquinone. More recently, a specific link between mitochondria and inflammation has been established, which, at least indirectly, further compromises mitochondrial energy production. Parkin and PINK1 deficiency leads to release of damage-associated molecular patterns from mitochondria, followed by a cGAS/STING-dependent activation of innate immunity, quantifiable by increased Interleukin 6 levels in mice but also in humans. While the most direct link between mitochondrial dysfunction and reduced energy production has been established for Parkin and PINK1, other PD-related proteins, such as LRRK2 and GBA, have also been implicated in mitochondrial impairment, adding another layer of complexity to the relationship between monogenic PD, mitochondria, and energy metabolism.

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Organizers: Vladimir S. Kostić (Belgrade, RS)

MANIPULATING NEURONAL CALCIUM HOMEOSTASIS PROTECT AGAINST SYMPTOMATOLOGY AND DEATH IN A PRIONLIKE ALPHA-SYNUCLEIN TRANSGENIC MOUSE OF PARKINSON'S DISEASE

Cristine Betzer, Nelson Ferreira, Lasse Reimer, Emil Gregersen, Asad Jan, Sara Elfarrash, Hjalte Gram, Nanna Møller Jensen, Marina Romero-Ramos, Poul Henning Jensen

Aarhus University, Dept. of Biomedicine & DANDRITE, Danish Research Institute of Translational Neuroscience, Aarhus, Denmark

phj@biomed.au.dk

Intraneuronal alpha-synuclein aggregation is closely linked to the pathophysiology of Parkinson's disease and the intercellular spreading hereof is considered to play a central role for the progression of the disease and its symptoms. We published that intracellular alpha-synuclein aggregation activates the ER-resident calcium pump SERCA thereby causing a redistributing of cytosolic calcium into the ER (Betzer, 2019, EMBO Report). Data will be presented of studies aiming at increasing cytosolic calcium in an attempt to reduce the cytotoxicity of intracellular alpha-synuclein aggregates. This strategy reduces cellular alpha-synuclein levels in vitro and protects against alpha-synuclein prion-like neurodegeneration and death in an alpha-synuclein transgenic mouse model.

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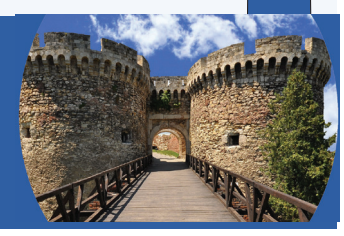

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OLD AND NEW FUNCTIONS OF THE MITOCHONDRIAL KINASE PINK1 TO PROMOTE NEURONAL SURVIVAL

Enza Maria Valente

Department of Molecular Medicine, University of Pavia, Pavia, Italy

enzamaria.valente@unipv.it

Mutations in the *PINK1* gene are the second most frequent cause of autosomal recessive Parkinson Disease (PD) after Parkin, and can represent a risk factor towards sporadic PD. The *PINK1* gene [Phosphatase and tensin homolog (PTEN)-induced kinase 1] encodes a mitochondrial serine/threonine kinase, which has been implicated in several functions, mostly aimed at protecting neuronal cells against different types of stress. Extensive studies identified PINK1 as a crucial player in the mitochondrial quality control pathway, required to label damaged mitochondria and promote their elimination through an autophagic process (mitophagy). Mounting evidences now indicate that PINK1 activities are not solely restricted to mitophagy, and that different subcellular and even sub-mitochondrial pools of PINK1 are involved in distinct signalling cascades to regulate cell metabolism and survival. We showed that, in conditions of mitochondrial damage, PINK1 selectively relocalizes at mitochondria-associated membranes (MAMs), where it recruits the proautophagic protein Beclin1, enhances mitochondria-ER contact sites and promotes the formation of omegasomes, that represent autophagosome precursors. Other proteins implicated in neurodegeneration (such as alpha-synuclein, parkin and DJ-1) were also recently localized at MAMs, and these specialized districts have been implicated in many key cellular events. In this light, the observed prevalent localization of PINK1 at MAM may well explain other neuroprotective activities of this protein, such as modulation of mitochondrial calcium levels, mitochondrial dynamics, and apoptosis. Interestingly, research on PINK1 has recently unravelled that its multiple functions extend well beyond neuroprotection, implicating this eclectic protein in a growing number of human pathologies, including cancer, diabetes, cardiopulmonary dysfunctions and inflammation.

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Organizers: Vladimir S. Kostić (Belgrade, RS)

TARGETING ENERGY-SENSING PATHWAYS AS POTENTIAL NEUROPROTECTIVE STRATEGY IN PD

Ivanka Marković[1], Maja Jovanović[1], Marija Dulović[1], Marija Jeremic[1], Ljubica Harhaji-Trajković[3], Vladimir Kostić[2] and Vladimir Trajković[3]

1Institute of Medical and Clinical Biochemistry, Faculty of Medicine, University of Belgrade;
2Institute of Biological Research "Siniša Stanković", University of Belgrade;
3Clinic for Neurology, Faculty of Medicine, University of Belgrade;
4Institute of Microbiology and Immunology, Faculty of Medicine, University of Belgrade

ivanka.markovic@med.bg.ac.rs

Aberrant mitochondrial homeostasis is an important contributor to neuronal demise in Parkinson's disease (PD). An increasing body of evidence shows that dysfunctional mitochondria and all of their resultant features are related to adenosine monophosphate-activated protein kinase (AMPK), main intracellular energy sensor and regulator of cellular processes such as autophagy and mitochondrial biogenesis. AMPK deregulation has been demonstrated in different PD models, as well as in the brains of PD patients, but whether AMPK activation in PD is beneficial or detrimental remains controversial. We investigated the role of AMPK signaling pathway in different cellular models of PD-related neurodegeneration (intra- and extracellular alpha-synuclein overexpression, application of parkinsonian mimetic 1-methyl-4-phenyl piridinium-MPP^+). Our results revealed that the activity of AMPK signalling pathway was altered in all the models, with alpha-synuclein causing decrease, whereas MPP^+ inducing increase in AMPK activity. Genetic downregulation of AMPK increased the sensitivity to harmful effect of alpha-synuclein (both secreted and nitrated or dopamine-modified) as well as MPP^+. Pharmacological restoration of AMPK activity, using AICAR and metformin, reduced the *in vitro* toxicity of ASYN overexpression, and also the level of MPP^+-induced cell death. However, it appears that AMPK neuroprotective effect may include distinct model-dependent mechanisms – effects on mitochondrial biogenesis rather then prosurvival kinase Akt activation in alpha-synuclein overexpression, whereas in MPP^+-induced damage AMPK activation protected SH-SY5Y cells through early activation of antioxidative Akt activity and late induction of cytoprotective autophagy. Taken together, these results suggest that modulation of AMPK activity may serve as a potential neuroprotective strategy in Parkinson's disease.

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Room Pacific

Symposium 25

GABA-ergic control of neuronal plasticity in the hippocampal dentate gyrus: functional implications

Organizers: Gal Richter-Levin (Haifa, IL) and Jelena Radulovic (Chicago, IL, USA)

SIGNALLING PATHWAYS INVOLVED IN SELECTIVE INHIBITORY SYNAPSE STABILIZATION

Hansjürgen Volkmer, Pauline Jeckel, Simone Beuter, Martin Kriebel

NMI at the University of Tübingen, Reutlingen, Germany

volkmer@nmi.de

Stabilization of GABAergic synapses is linked to the clustering of the postsynaptic scaffolding protein gephyrin. We applied a genome-wide screen to identify genes required for the clustering of gephyrin. Among the hits, we found several receptor tyrosine kinases (RTK) potentially involved in gephyrin clustering. Here we provide evidence for a function of RTKs trkB, FGFR1 and EphA7 signaling for the stabilization of GABAergic synapses in vitro and in vivo. These receptors control interneuron connectivity specifically in different subcellular neuronal compartments. trkB and EphA7 are involved in the stabilization of proximal dendritic and somatic GABAergic synapses while neurofascin/FGFR1 interactions account for axo-axonic synapses. RTK-mediated gephyrin clustering relies on PI3K-Akt and MAPK pathways and involves the activation of mTOR. mTOR is an interaction partner of gephyrin as shown by co-immunoprecipitation. The activation state of mTOR regulates the mTOR-gephyrin interaction. Likewise, mTOR activation after TSC2 knockdown or mTOR inhibition by rapamycin induce or inhibit gephyrin clustering, respectively. mTOR activation was suggested to occur at late endosomes. Accordingly, interference with the endosomal pathway by overexpression of dominant-negative and constitutively active Rab5 impairs gephyrin clustering in primary hippocampal neurons. In conclusion, we provide evidence for a role of RTKs in the complex regulation of interneuron connectivity.

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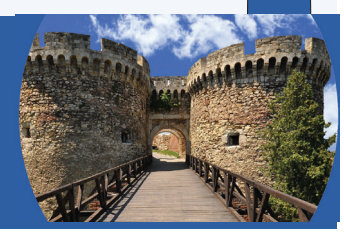

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GABAERGIC MECHANISMS IN THE HIPPOCAMPUS CONTROLLING FEAR MEMORY STRENGTH AND SPECIFICITY

Oliver Stork

Department of Genetics and Molecular Neurobiology, Institute of Biology, and Center of Behavioral Brain Sciences, Otto-von-Guericke University Magdeburg, Germany

oliver.stork@ovgu.de

Aims: Pavlovian fear conditioning is an established learning paradigm that allows studying neural mechanisms of fear and anxiety in various species and that may be employed to emulate specific aspects of anxiety disorders.

Methods: We investigated, in mice, molecular and physiological processes in the amygdalo-hippocampal system that are involved in the consolidation and reconsolidation of long-term fear memory.

Results: GABAergic interneurons are of critical importance for these processes, as indicated by the hyperarousal, fear generalization and deficit in fear extinction of mice deficient for the key enzyme in GABA synthesis, glutamic acid decarboxylase 65. We observed specific changes in the expression of glutamic acid decarboxylase and other interneuron-specific factors in hippocampal subfields following the acquisition and reconsolidation of fear, and in response to the enhancement of fear conditioning in a juvenile stress model of PTSD. Observed changes in gene expression were attributed to specific subpopulations of GABAergic interneurons and their role fear memory-induced alterations of local circuit activity of hippocampal subfields. Genetic and chemogenetic manipulation of these interneuron populations resulted in alterations of spontaneous and induced network activity, including sharp wave ripples and gamma oscillations, that were associated with fear memory generalization and lack of fear extinction in the behaving animals.

Conclusions: We have been able to dissect local circuits in the hippocampus that control specific aspects of fear memory formation and encoding of memory salience. Our data demonstrate a role of GABAergic interneurons in the hippocampus in the development of pathological fear memory and its physiological network correlates.

Supported by the German Research Foundation and the Sate of Sachsonia-Anhalt

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STRESS MODULATION OF HIPPOCAMPAL ACTIVITY-SPOTLIGHT ON THE DENTATE GYRUS

Gal Richter-Levin

The Integrated Brain and Behavior Research Center (IBBR);
University of Haifa, Haifa, Israel

galrichterlevin@gmail.com

Traditionally, research of the hippocampus focused on the hippocampus proper, probably because of the distinctive nature of CA1 and CA3 place cells. The dentate gyrus (DG) was often referred to as a gateway to the hippocampus proper. However, the identification of active neurogenesis specifically within the DG, and the association of neurogenesis with memory, stress and mood disorders, has led in recent years to growing interest in DG role and function. We have previously demonstrated that exposure to stress differentially affects long term potentiation (LTP) and local circuit activity in the DG and CA1. We further found that priming the basolateral amygdala (BLA) differentially affects plasticity in CA1 and the DG in a similar way. More recently we could demonstrate that selective and local alterations of GABAergic functioning within the DG was sufficient to impact emotional behavior and learning under stress. The findings indicated also differences between the role of the dorsal and ventral DG. Distinguishing between stress vulnerability and stress resilience indicated that GABAergic functioning in the dorsal DG was associated more with stress resilience while that in the ventral DG with vulnerability to stress. Taken together, the results indicate that the dentate gyrus (DG) of the hippocampus is likely to play a pivotal role in defining the impact of stress on hippocampal functioning. The DG is a dynamic structure, responsive to stress, but unlike the CA1, it differentiates between different types of stressful experiences. There are significant differences between the involvement of the dorsal and ventral DG in responding to stress and these differences are likely to contribute to the diverse effects of stress on memory formation.

This work was supported by research grant no. 3-13563 from the State of Israel Ministry of Science, Technology, & Space to GR-L, by a DFG grant STO 488/6-1 to OS and GR-L. and by an ISF award no. 1517/16 to GR-L.

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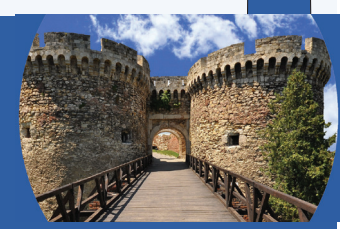

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OXYTOCIN RECEPTOR-POSITIVE INTERNEURONS IN THE DENTATE GYRUS LINK STRESS-RELATED MEMORIES TO SOCIAL BEHAVIOR

Mariah Meyer, Gianmaria Maccaferri, and Jelena Radulovic
Northwestern University, Chicago, IL, USA
j-radulovic@northwestern.edu

Stress-related memories sometimes exert a negative impact on social behavior even when they are not readily accessible for retrieval. For example, patients suffering from traumatic amnesia in response to overwhelming or repeated stress, often develop social deficits, such as reduced sociability, isolation, or social disfunction. This phenomenon is predominant in males, whereas females mainly develop affective symptom. To study the neurobiology of memory-induced social disfunction, we developed a model of state-dependent, fear-inducing context memory in mice resulting in impaired sociability in males but not females. Using circuit tracing and silencing approaches, we demonstrated that this social deficit is mediated by oxytocin receptor-positive interneurons in the hilus of the dentate gyrus, which innervate dentate gyrus granule cells interacting with neurons in the lateral septum. Thus, by modulating activity of long-range projections, a local oxytonergic network can impact behavior based on stress-related memories.

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Room Atlantic 1

Symposium 26

Psychotic disorders – progress in identifying the biological substrates of a complex presentation

Organizers: Jeremy Hall (Cardiff, UK), Nadja P. Maric (Belgrade, Serbia) and Society of Biological Psychiatry (Serbia)

INVESTIGATING THE GENETIC BASIS OF PSYCHOTIC DISORDERS BASED ON RISK MEDIATED THROUGH CALCIUM CHANNELS

Jeremy Hall

Neuroscience and Mental Health Research Institute (NMHRI), Cardiff University, United Kingdom

HallJ10@cardiff.ac.uk

Voltage gated calcium channels have been strongly implicated in psychiatric disorders. In this presentation I will present data on a model of low dosage of the voltage gated calcium channel cacna1c. I will show how decreased dosage of this channel results in specific behavioural changes in fear processing. I will also show that this is associated with specific molecular and electrophysiological changes in the hippocampus. Finally I will present evidence that agonists of the neurotrophic receptor TrkB/C can overcome these behavioural molecular and physiological deficits.

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NEUROCHEMICAL IMAGING IN FIRST EPISODE PSYCHOSIS AND ANTIPSYCHOTIC RESPONSE

Sameer Jauhar

Department of Psychological Medicine, King's College, London, United Kingdom

sameer.jauhar@kcl.ac.uk

The presynaptic dopamine system has been implicated in the etiology of psychotic disorders, and molecular imaging has suggested a relationship between this and antipsychotic response in established schizophrenia. In this symposium I will present data from a number of PET studies we have conducted in people with first episode psychosis, showing trans diagnostic abnormalities of this system across the illness constructs of bipolar disorder and schizophrenia, as well as a relationship between this system and antipsychotic response in people presenting with their first episode of psychotic illness. Finally, I will present recent, previously unpublished data on the effects of antipsychotics on both the presynaptic dopamine system and measures of glutamate, as measured by magnetic resonance spectroscopy.

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LIPIDOMICS, BIOMARKERS, AND SCHIZOPHRENIA: A CURRENT PERSPECTIVE

Ljubica Tasic

Laboratory of Biological Chemistry, Organic Chemistry Department, Institute of Chemistry, University of Campinas (UNICAMP), Campinas, SP, Brazil

ljubica@unicamp.br

Lipidomics is a lipid-targeted approach aiming at comprehensive analysis of lipids in biological systems, which with a progress in analytical techniques have gain power in preventive and therapeutic human health problems solving. This talk aims to illustrate how lipidomics can contribute to better understanding of the biological mechanisms inherent to schizophrenia and why lipids are relevant biomarkers of schizophrenia. Also, the future perspectives of lipidomics in mental disorders are going to be discussed. On the other side, in the multi-factorial complexity of psychotic disorders, such as in schizophrenia, identification of metabolic markers would be of extreme relevance not only to assist in an early detection and diagnosis of the disorder, but also to subsequently facilitate disease monitoring and treatment responses. Metabolic markers in diagnosis are thought to be one of the most fascinating categories of biomarkers. Since a biomarker should be detected and measured in a sample obtained using noninvasive procedures, body fluids including blood plasma/serum, urine, saliva and, in some extent, cerebrospinal fluid are thought to be ideal sources for biomarker monitoring. To date, numerous studies have utilized metabolomics to better understand psychotic disorders and findings from these studies have begun to converge.

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TRANSGRESSING BOUNDARIES: UNIFYING CONCEPTS FOR PREVENTING AND TREATING COMPLEX DISORDERS FROM SCHIZOPHRENIA TO DEMENTIA - TO ECOSYSTEM DAMAGE

Mark J Millan

CTI Neuropsychiatry, IDR Servier, Croissy/Seine, France

mark.millan@servier.com

Silos are omnipresent in the world of Research and Development for CNS disorders, such as the artificial divide between Psychiatry and Neurology, the translational cleft from the preclinical to the clinical, limited communication between cellular *vs in vivo* specialists, a focus on only certain classes of GPCR or neurotoxic protein, and the predilection of a lab for just one specific model or technology. Most people recognize - as for environmental degradation, loss of biodiversity and climate change - the importance of the issue. However, likewise by analogy, too little is happening in resolve the problem. One example is the partitioning of neurodevelopmental *vs* neurodegenerative disorders into different working domains despite numerous communalities as regards clinical symptoms, neural substrates, risk genes, pathological changes and even potential therapies, as well as a mutual need for robust biomarkers and both symptomatic and course-altering therapies[1]. This talk highlights how studies in psychosis and dementia might be better aligned, focusing on two complementary examples. *First*, the potential utility of combined dopamine D_3/5-HT_6 antagonists for treatment of cognitive and other deficits of schizophrenia and Alzheimer's disease[1]. *Second*, the use of digital measurement technologies to improve the monitoring and, ultimately, control of deficits in social cognition common to schizophrenia, Alzheimer's disease and other classes of CNS disorder (an EU/IMI-funded PRISM" project).[2] A further "boundary" will also be transgressed, between disorders of the *brain* and those of another complex network, *coral reefs*, both under threat from multiple-recurrent stressors like climate change, and both urgently requiring improved protection.

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SYMPOSIUM 27

OBSERVING NEURONAL COMPUTATION DURING BEHAVIOR WITH LARGE-SCALE IMAGING METHODS

Organizers: Balazs Rozsa (Budapest, HU)

THERAPEUTIC USE OF NEUROPROSTHETICS BASED ON ORGANIC ELECTRONICS

Williamson Adam

INS - Institut de Neurosciences des Systèmes, UMR INSERM 1106, Aix-Marseille Université, Faculté de Médecine La Timone, Marseille, France

adam.WILLIAMSON@univ-amu.fr

My research on organic neuroprosthetics is primarily to improve the treatment of epilepsy by prototyping devices which could provide relief to patients suffering from drug-resistant or surgically untreatable seizures. However, the impact of the minimally-invasive technology with organic electrodes and transistors includes all branches of clinical and non-clinical neuroscience involved in 1) Electrode-based Brain stimulation for the therapeutic treatment of other neurodegenerative diseases, 2) Imaging of large-area neural networks with multiphoton systems seeking combined simultaneous electrophysiology, and finally 3) Drug delivery for the therapeutic treatment of other neurodegenerative diseases (most obviously Parkinson's disease). In this presentation I will detail the use of devices in the treatment of epilepsy, and highlight devices in the other 3 major categories.

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OBSERVING NEURONAL COMPUTATION DURING BEHAVIOR WITH LARGE-SCALE IMAGING METHODS

Organizers: Balazs Rozsa (Budapest, HU)

MULTI-SITE VOLTAGE AND CALCIUM IMAGING REVEAL DENDRITIC SPIKES ALONG THIN APICAL DENDRITES OF CORTICAL PYRAMIDAL NEURONS

Michael Castañares, Greg Stuart and Vincent Daria

Eccles Institute of Neuroscience, John Curtin School of Medical Research, The Australian National University, ACT, Australia

vincent.daria@anu.edu.au

We use holographically projected light to simultaneously record dendritic activity of cortical pyramidal neurons. Spatially encoding a phase hologram on a laser produces multiple foci, which can be arbitrarily directed onto different dendritic regions of the neuron. Each focus excites neuronal activity reporters via two-photon(2P) or single-photon (1P) multi-foci excitation. The fluorescence emanating from all foci are simultaneously recorded using an electron-multiplying charge-coupled device (EMCCD) camera thereby enabling simultaneous multi-channel recording of the neuronal activity from multiple sites at high frame rates (up to 400Hz). We used two types of reporters: (1) calcium indicator, Cal520; and (2) voltage indicator, JPW1114. Using these two imaging techniques, we report the generation of dendritic calcium spikes in thin apical oblique dendrites evoked by low-frequency bursts of back-propagating action potentials (bAPs). We observed a non-linear (step-wise) increase in calcium influx into specific oblique dendrites during 50 to 80Hz bursts of bAPs. At the same critical frequency range, we also observed a step-wise increase in the after-depolarizing potential (ADP) at the soma by ~4mV. These results indicate that dendritic calcium spikes can be evoked in thin oblique dendrites of cortical layer 5 pyramidal neurons during somatic bursts action potentials in the frequency range between 50-80Hz. Oblique dendrites may therefore act as an independent domain for dendritic computation, with a critical frequency that is lower compared to that in the basal and in the nexus of the apical tuft.

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Room Atlantic 2

SYMPOSIUM 27

OBSERVING NEURONAL COMPUTATION DURING BEHAVIOR WITH LARGE-SCALE IMAGING METHODS

Organizers: Balazs Rozsa (Budapest, HU)

CORTEX-WIDE ACTIVATION OF VIP-EXPRESSING INHIBITORY NEURONS BY REWARD AND PUNISHMENT

Adam Kepecs

Cold Spring Harbor Laboratory, New York, United States

kepecs@cshl.edu

Reward and punishment powerfully inform ongoing behaviors and drive learning throughout the brain. If reward and punishment signals are broadly distributed across cortex, it is important to identify how these global signals exert influence over local cortical computations. Previously we found that VIP-expressing cortical inhibitory neurons specialize in local gain-control and also respond to reward and punishment, in auditory cortex. Here we used 3D random-access two-photon microscopy and fiber photometry to monitor VIP neural activity in dozens of cortical areas while mice performed an auditory decision task. Most VIP interneurons cortex-wide were robustly activated by water reward and air-puff punishment, and were modulated by arousal states. Primary visual cortex VIP interneurons also showed orientation- and direction- selective responses. Taken together with the role of VIP neurons in local circuit disinhibition, these results suggest that VIP neurons may provide a means by which global reinforcement signals influence local circuit computations and their plasticity.

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Room Atlantic 2

Symposium 27

Observing neuronal computation during behavior with large-scale imaging methods

Organizers: Balazs Rozsa (Budapest, HU)

FAST 3D IMAGING BY 3D ACOUSTO-OPTICAL MICROSCOPY REVEALED SPATIOTEMPORALLY ORCHESTRATED CLUSTERS IN THE VISUAL CORTEX

Gergely Szalay[1], Zoltán Szadai[1], Linda Judák[1], Pál Maák[3], Katalin Ócsai[2], Máté Veress[3], Tamás Tompa[1], Balázs Chiovini[1], Gergely Katona[1,2], Balázs Rózsa[1,2]

1 Laboratory of 3D functional network and dendritic imaging, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary;
2Pázmány Péter Catholic University, Budapest, Hungary;
3Department of Atomic Physics, Budapest University of Technology and Economics, Budapest, Hungary

rozsabal@koki.hu

Our long-term aim is to assess the feasibility of creating an "artificial sense" and, thereby, a sensory (visual) prosthetic. While working towards this goal, we need to develop novel technologies which can simultaneously stimulate and record the fast activity of large neuronal assemblies in large scanning volumes. With some novel developments in the 3D AO scanning technique and great achievements in optics (Figure 1a, 1b) now it is possible to image more than 2000 neurons simultaneously in entire cortical columns and in separate cortical areas with high spatial (up to 500nm, in the center) and temporal (up to 50kHz/ROI) resolution in several cubic millimeter volumes (up to $4\times4\times1mm^3$) in 3D. 3D AO imaging provides a more than 10^6-fold increase in signal collection efficiency and measurement speed compared to the classical raster scanning method [1-5]. The relatively broad wavelength range (920-1100 nm) of the new telescope (Figure 1a) and the mesoscope objective (Figure 1b) allowed for the 3D imaging of entire cortical columns. We found that, in contrast to previous theories, the brain of adult mice is plastic, as visual representation (e.g orientation tuning) can dynamically change as a function of time at multiple temporal scales following visual learning in individual spines and neurons (Figure 2) and neurons with similar orientation sensitivity changes are forming spatially overlapping clusters.

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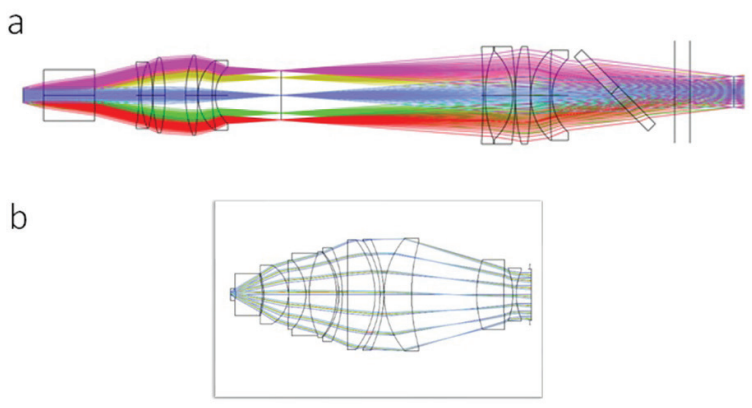

Figure 1. *a) Optical layout of the projection lens assembly developed to project the 3D AO scanner to the objective. b) Optical layout of the mesoscopic objective (NA=0.8, FOV=5 mm).*

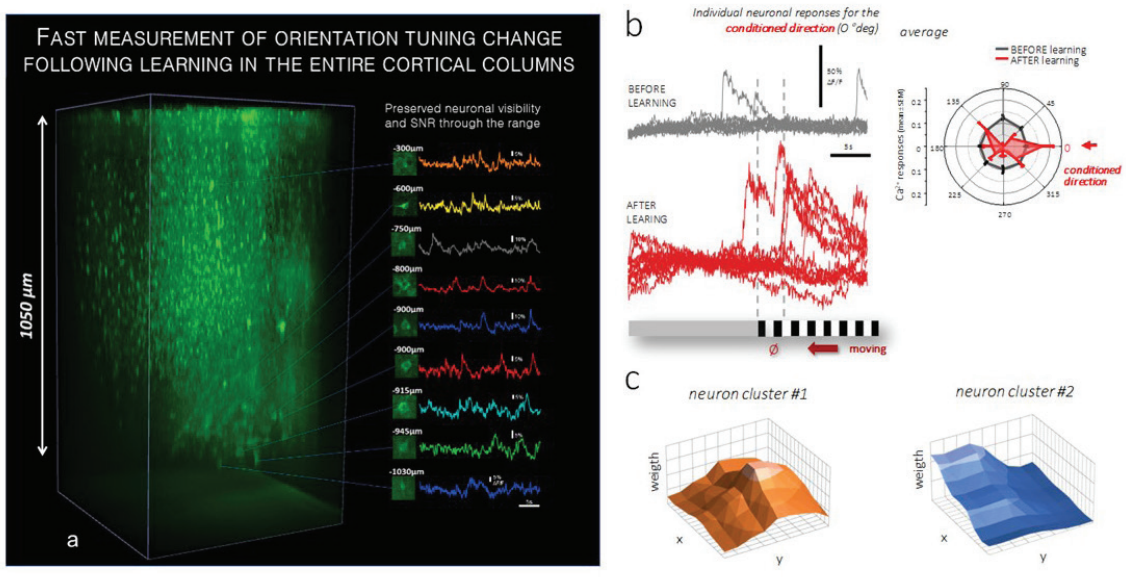

Figure 2. *a) Imaging entire cortical columns in > 1 mm z scanning range b) in contrast to well accepted theories visual responses change following learning. c) These dynamic changes are happening in spatially overlapping clusters of neurons, figure shows the centers of weight of the clusters measured simultaneously.*

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Room Mediterranean

SYMPOSIUM 28

GENDER ISSUES IN NEUROSCIENCE RESEARCH

Organizers: Anastasia S. Tsingotjidou (Thessaloniki, GR)

GENDER OF LABORATORY ANIMALS IN NEUROSCIENCE

Klas Abelson

Department of Experimental Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

klasab@sund.ku.dk

The use of laboratory rodents in biomedical *in vivo* research has historically mainly involved male subjects. The reason for not including female subjects has often been explained by concerns of increased variation due to the oestrus cycle-related hormonal fluctuations in the in female rodents, as well as due to concerns about the considerable size of the experiment, when both sexes are included. However, numerous studies have in recent time demonstrated sex related differences in the animals' response from experimental testing. Neglecting this fact in neuroscience where experimental animals are involving may lead to an impaired understanding of the basic mechanisms controlling our nervous system; the pathogenesis of diseases and the possible treatment of the same. This in turn may result in a lower translational validity in clinical trials. Taking both genders into consideration is thus a necessity in all biomedical research. Even though this requires an increased size of the experiment, a proper experimental design can overcome most obstacles. This presentation will give some examples of gender related differences in animal experiments, and present some possible methods experimental design that can facilitate the inclusion of both male and female subjects, to increase the translational value of neuroscience research.

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GENDER ISSUES IN NEUROSCIENCE RESEARCH

Organizers: Anastasia S. Tsingotjidou (Thessaloniki, GR)

GENDER BIAS IN PAIN BASIC RESEARCH: RECENT DATA

Anastasia Tsingotjidou

Laboratory of Anatomy, Histology and Embryology, School of Veterinary Sciences, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece

astsing@vet.auth.gr

Pain is a unique phenomenon that is simultaneously unpleasant and essential affecting the body and/or the soul. Men and women diverge in their responses to pain. Research is being done for years for gender differences both in nociception and its underlying mechanisms, and also in the response of pain treatment. The last two decades scientists are paying more attention to the gender of the experimental animals being used for both the basic and clinical pain research. Thorough studies on the differentiated gender use of laboratory animals exist in order to extrapolate conclusions in pain perception and modulation. This presentation will focus on the conclusions of these studies and present how these have affected pain management as well.

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Symposium 28

Gender issues in neuroscience research

Organizers: Anastasia S. Tsingotjidou (Thessaloniki, GR)

SEX DIFFERENCE IN ANIMAL MODELS OF PSYCHIATRIC DISORDERS

Milos Mitic[1], Zeljka Brkic[1], Zorica Petrovic[1], Minja Milosavljevic[1], Emilija Glavonic[1], Ester Francija[1], Iva Lukic[1], Jelena Radulovic[2] and Miroslav Adzic[1]

1Department of Molecular Biology and Endocrinology, VINCA Institute of Nuclear Sciences, University of Belgrade, Serbia;
2Department of Psychiatry and Behavioural Sciences, The Asher Center of Study and Treatment of Depressive Disorders, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA

milos.mitic@vinca.rs

Psychiatric disorders are well defined by sex differences regarding their prevalence, manifestation and pharmacotherapy. Epidemiological studies and recent meta-analyses corroborate that women are approximately twice as likely susceptible to stress-related psychopathologies than men. Also, women tend to show poorer response rates and slower clinical improvement with tricyclic treatment, while appear to respond better to selective serotonin reuptake inhibitors. Despite ongoing research efforts, our understanding of the etiology and pathophysiology of psychiatric disorders remains limited and current pharmacotherapies are efficacious for only a subpopulation of individuals. At the same time, preclinical studies on animal models of depression and antidepressant response have provided insights with regard to sex differences that could be useful for the design and interpretation of future clinical trials. However, majority of preclinical pharmacological studies mostly employs male animals, so there is an increasing need to validate different animal models of psychiatric disorders that include both males and females. Taking in consideration the complexity and heterogeneity found in etiology of psychiatric illnesses, a focus of animal studies has been devoted to investigate the role of sex differences and their influence of behavioral changes and physiological processes that are impaired in these disorders, such are neurotransmission, activity of hypothalamic–pituitary–adrenal (HPA) axis, inflammatory processes and neuroplasticity. We highlight the need to incorporate both male and female animals in experimental studies aiming at sex-oriented prevention, diagnosis and therapy of psychiatric disorders.

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SYMPOSIUM 28

GENDER ISSUES IN NEUROSCIENCE RESEARCH

Organizers: Anastasia S. Tsingotjidou (Thessaloniki, GR)

NON-EXPERIMENTAL RESEARCH VARIABLES IMPACTING GENDER-BASED RESEARCH

Patrick Sharp

Animal Resources Authority, Perth, Australia;
Adjunct Professor, Murdoch University, School of Veterinary and Life Sciences, Perth, Australia

psharp@arc.wa.gov.au

An animal's gender is a significant component and concern that may impact biomedical research. Gender's impact may be broadly categorized as endogenous (relating to the gender) or exogenous (factors that may act to alter an animal's gender). The presentation will highlight and discuss these endogenous and exogenous gender research impacts.

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SYMPOSIUM 29

MOLECULAR FACTORS OF NEUROREPAIR

Organizers: Igor Jakovcevski (Köln, DE) and Pavle Andjus (Belgrade, RS)

INTERFERENCE WITH ENDOGENOUS ERK INHIBITORS AS NOVEL TREATMENT STRATEGY FOR NEUROLOGICAL DISEASES

Barbara Hausott, Letizia Marvaldi, Sitthisak Thongrong, Jong-Whi Park, Lars Klimaschewski

Division of Neuroanatomy, Department of Anatomy and Histology, Medical University of Innsbruck, Austria

lars.klimaschewski@i-med.ac.at

Intracellular negative feedback inhibitors of receptor tyrosine kinase signaling, such as the Sprouty (Spry) proteins, play a key role in development and maintenance of the nervous system. Sprouties function as growth factor antagonists by specific interference mainly with processes upstream of extracellular regulated kinases (see figure). Applying three different in-vivo lesion models we demonstrate that reduction of Spry2 and -4 in neurons and glial cells promotes neuronal survival and axonal regeneration in the central and peripheral nervous system. Injection of Spry2/4 siRNAs into rat brains reduces the lesion size in response to endothelin-induced vasoconstriction (a model for stroke) three weeks after the injury. In kainate-induced epileptogenesis, secondary brain damage is decreased as well. Heterozygous Spry2/4 knockout mice exhibit reduced neuronal loss three weeks after kainate injection into the hippocampus which is accompanied by increased astrocytosis and reduced neuronal migration (dispersion of granule cells). In the peripheral nervous system, primary sensory neurons dissociated from Spry2 knock-out ganglia reveal stronger ERK activation and enhanced axon outgrowth. Following sciatic nerve crush, significantly more myelinated axons regenerate in $Spry2^{+/-}$ mice which is accompanied by faster recovery of sensomotor performance, higher number of motor endplates in distal muscles and increased expression of GAP-43. Taken together, our results suggest a role for Spry2 as a potential target for pharmacological inhibition to accelerate long-distance regeneration in peripheral nerves and to promote long-term neuronal survival in neurological disease.

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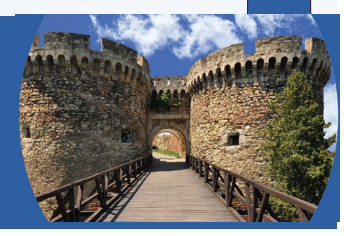

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SYMPOSIUM 29

MOLECULAR FACTORS OF NEUROREPAIR

Organizers: Igor Jakovcevski (Köln, DE) and Pavle Andjus (Belgrade, RS)

PROTEOLYTIC PROCESSING OF CELL ADHESION MOLECULE L1 (L1CAM) IN NERVOUS SYSTEM DEVELOPMENT AND REGENERATION

David Lutz

Department of Neuroanatomy and Molecular Brain Research, Ruhr University Bochum, Germany

david.lutz@rub.de

Aims: The cell adhesion molecule L1 (L1CAM) does not only „keep cells together" by homophilic and heterophilic interactions, but L1 can also promote cell motility when cleaved by several proteases into fragments. L1 fragments are generated at the plasma membrane. Some of these fragments are released into the extracellular space, whereas other membrane-bound fragments are internalized via the subcellular traffic circuits and enter the nucleus, thus conveying extracellular signals to the cell interior. The present work aims at studying the effect of L1-proteolysis on morphogenic events during nervous system development and regeneration.

Methods: Genome-wide editing via zinc finger nucleases was used to generate mice with a mutation that abolishes cleavage of L1 by proteases targeting L1's third FNIII-like repeat.

Results: Mice with a mutation that abolishes cleavage of L1 develop congenital ventriculomegaly characterized by improperly anchored ependymal cell cilia, and altered distribution of the axonal projections along the nigro-striatal axis. Viral re-introduction of proteolytic L1 fragments into L1 mutants *in utero* at critical neurodevelopment stages led to partial rescue of the congenital ventriculomegaly due to correction of the the ependymal cell cilia anchorage.

Conclusions: Stimulation of proteolysis of L1 via injection of L1-fragments or proteases active on L1 or L1 mimetics is beneficial for development and regeneration of the diseased nervous system.

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SYMPOSIUM 29

MOLECULAR FACTORS OF NEUROREPAIR

Organizers: Igor Jakovcevski (Köln, DE) and Pavle Andjus (Belgrade, RS)

EMBRYONIC LOSS OF HCN/H-CHANNEL FUNCTION IN MOUSE FOREBRAIN RESULTS IN IMPAIRED NEURAL PROGENITOR PROLIFERATION AND MICROCEPHALY

Anna Katharina Schlusche[1,2,¶], Sabine Ulrike Vay[3], Malte Stockebrand[1,2], Maria Adele Rueger[3,4], Dirk Isbrandt[1,2,4], Igor Jakovcevski[1,2,4]

1German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany;
2Institute for Molecular and Behavioral Neuroscience, University of Cologne, Cologne, Germany;
3Department of Neurology, University Hospital of Cologne, Cologne, Germany.;
4Center for Molecular Medicine Cologne, University of Cologne, Cologne, Germany

igor.jakovcevski@dzne.de

Aims. Developmental and evolutionary expansion of the cerebral cortex relies on the controlled division of neural stem and progenitor cells. Here, we report on the previously unrecognized role of hyperpolarization-activated, cyclic nucleotide-gated cation (HCN) channels in regulating the proliferation of neural progenitors during forebrain development. HCN channel subunits are expressed by human and murine neural stem and progenitor cells.

Methods. Early embryonic ablation of HCN function restricted to the forebrain of mice under the control of EMX1 promoter lead to pronounced microcephaly and reduced neonatal survival rate.

Results. These effects were specific to early embryonic blockade of HCN-channel function. Loss of the HCN-channel current (*Ih*) impaired neural stem cell proliferation by affecting cell cycle progression, resulting in an G1 accumulation of neural progenitor cells shown by single cell transcriptome analysis. It also affected cell differentiation leading to earlier expression of glial markers.

Conclusions. Our data support the hypothesis that HCN channels are important intrinsic regulators of the proliferation and differentiation of neural progenitors, and that mutations in HCN channel genes could lead to severe brain malformations.

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Symposium 29

Molecular factors of neurorepair

Organizers: Igor Jakovcevski (Köln, DE) and Pavle Andjus (Belgrade, RS)

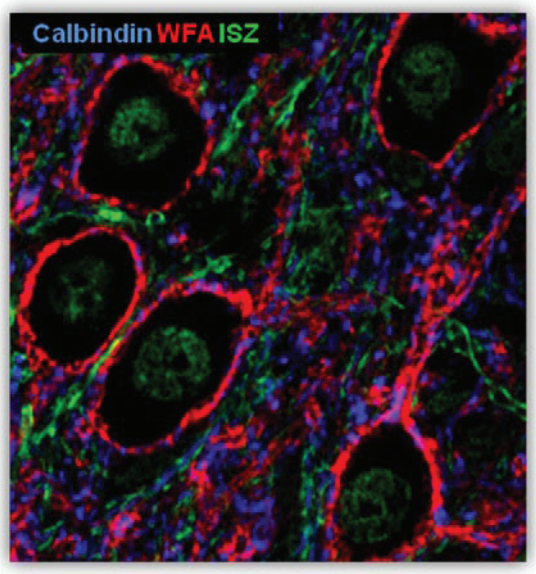
TENASCIN-C IN NEURONAL PLASTICITY AND REPAIR

P.R. Andjus[1]

Center for Laser Microscopy, Department of Physiology and Biochemistry, Faculty of Biology, University of Belgrade, Serbia

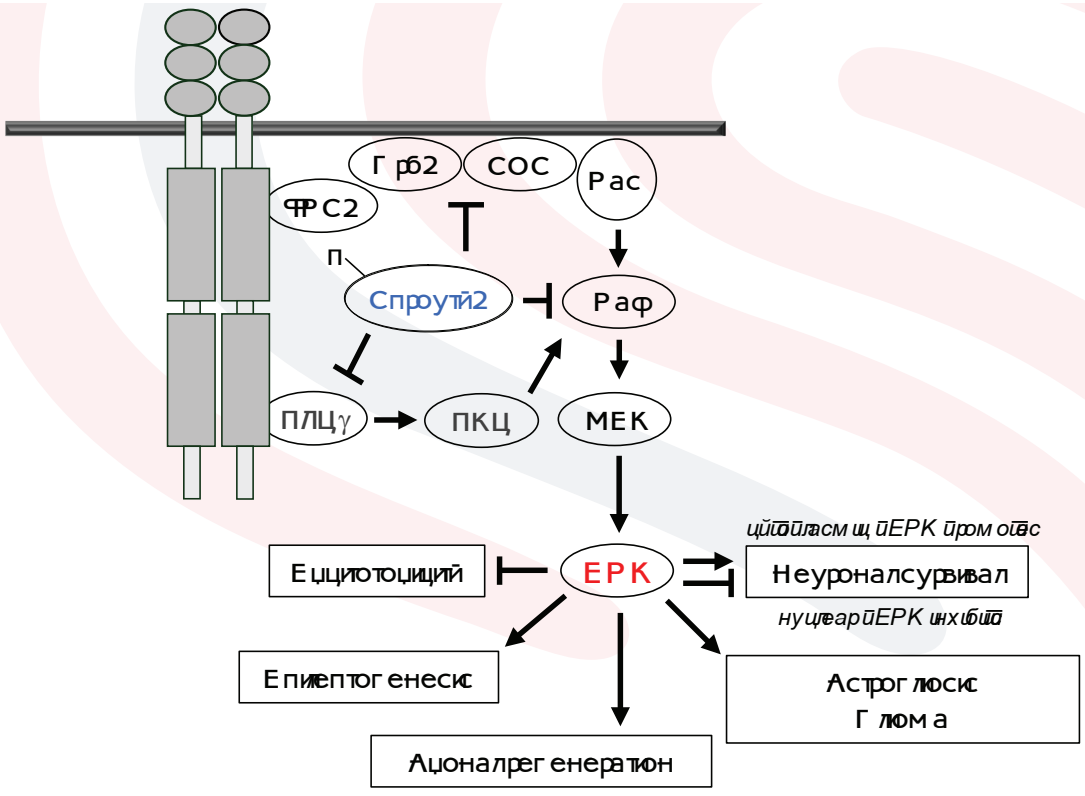
pandjus@bio.bg.ac.rs

The extracellular matrix glycoprotein tenascin-C (TnC) is widely expressed during development, while in the adult CNS its expression is downregulated except in areas of active plasticity and neurogenesis. We examined the role of TnC under conditions of enriched environment (EE) by observing the distribution of perineuronal nets (PNN) and the involvement of matrix metalloproteases (MMPs) in TnC-/- mice cerebral cortex. TnC role in adult neurogenesis (tested by BrdU, Ki67 and Dcx) was also followed (subgranular zone of the dentate gyrus). The molecular markers of plasticity were confirmed by a broad battery of behavioural tests. Finally we have tested the effect of fragments of TnC in (Fn A, FnC, FnD, Fn6-8 and EGF-L) the *in vitro* model of glial scar ("scratch wound") and *in vivo* model of spinal cord lesion. A significant tissue-selective reduction of PNN with MMP9 involvement (already at 4 weeks of EE) was revealed in TnC+/+ mice after 8 weeks of EE. The EE-induced pattern of synaptic coverage changed with TnC deficiency. Neurogenesis was stimulated by EE this effect being attenuated by TnC. At the behavioural level TnC deficiency was shown to attenuate the EE capability to modify complex learning functions. Studies of TnC fragments revealed a particular role for FnD in slowing down wound healing *in vitro* and *in vivo* and promoting activated microglia in the latter case. Our studies thus emphasize the importance of TnC in the adaptive response to environmental complexity and reveal the individual role of its fragments, in particular FnD in wound healing.



STRUCTURAL PLASTICITY

BEHAVIORAL PLASTICITY



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Room Pacific

SYMPOSIUM 30

NEUROEPIGENETICS AND BRAIN DISORDERS

Organizers: Marija Kundakovic (New York, NY, USA)

PM20D1 - A DISEASE-RELEVANT CHROMATIN LOOP IN ALZHEIMER'S

Johannes Gräff

Brain Mind Institute, School of Life Sciences, Ecole Polytechnique Fédérale Lausanne (EPFL), Lausanne, Switzerland

johannes.graeff@epfl.ch

Aims: The chances to develop Alzheimer's disease (AD) result from a combination of genetic and non-genetic risk factors, the latter likely mediated by epigenetic mechanisms. In the past, genome-wide association studies (GWAS) have identified an important number of risk loci associated with AD pathology, but a causal relationship thereof remains difficult to establish. In contrast, locus-specific or epigenome-wide association studies (EWAS) have revealed site-specific epigenetic alterations and thereby provide mechanistic insights for a particular risk gene, but often lack the statistical power of GWAS.

Methods and Results: Combining both approaches, we have found that *PM20D1* is a methylation/expression quantitative trait locus (mQTL/eQTL) coupled to an AD-risk associated haplotype, which displays enhancer-like characteristics and contacts the PM20D1 promoter via a haplotype-dependent, CTCF-mediated chromatin loop. Furthermore, PM20D1 is increased following AD-related neurotoxic insults, at symptomatic stages in the APP/PS1 mouse model of AD and in human AD patients, who are carriers of the non-risk haplotype. Importantly, genetically increasing and decreasing the expression of PM20D1 reduces and aggravates AD-related pathologies, respectively.

Conclusions: These findings suggest that in a particular genetic background, PM20D1 contributes to neuroprotection against AD.

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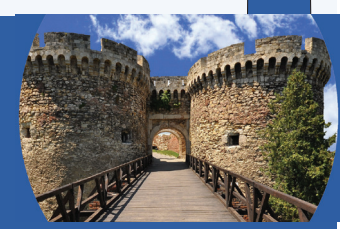

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Room Pacific

SYMPOSIUM 30

NEUROEPIGENETICS AND BRAIN DISORDERS

Organizers: Marija Kundakovic (New York, NY, USA)

EPIGENETIC ETIOLOGY OF INTELLECTUAL DISABILITY: FOCUS ON THE RUBINSTEIN-TAYBI SYNDROME

Angel Barco, Beatriz del Blanco, Michal Lipinski and Rafael Muñoz-Viana

Instituto de Neurociencias de Alicante (Universidad Miguel Hernández - Consejo Superior de Investigaciones Científicas), Alicante, Spain

abarco@umh.es

Many neurodevelopmental disorders associated with intellectual disability are caused by mutations in genes encoding chromatin-modifying enzymes. One of such syndromes is the Rubinstein-Taybi syndrome (RSTS, OMIM #180849), a congenital autosomal-dominant caused by hemizygous mutations in either one of the paralog genes *CREBBP* and *EP300*. The lysine acetyltransferases (KAT) CREB binding protein (CBP) and E1A binding protein (p300) encoded by these genes are both essential for the normal development of the nervous system. However, their specific roles regulating gene expression in developing and mature neurons remain poorly understood. To investigate these functions, we produced strains of inducible and tissue restricted knockout mice in which we remove either one or both proteins at different stages of neuronal development. Our experiments unveil the specific roles of these chromatin-modifying enzymes in neuronal differentiation, maturation, maintenance and plasticity.

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Symposium 30

Neuroepigenetics and brain disorders

Organizers: Marija Kundakovic (New York, NY, USA)

SEX-SPECIFIC EPIGENETIC REGULATION AND PSYCHIATRIC DISORDERS

Marija Kundakovic

Fordham University, Bronx, New York, USA

mkundakovic@fordham.edu

Anxiety and depression affect 20% of the world's population and are two times more prevalent in women than men. Natural sex-hormone fluctuation in females is likely the major contributor to this sex disparity, although the mechanism(s) are poorly-understood. We hypothesized that sex hormones dynamically affect epigenetic mechanisms in the brain contributing to inherent, female-specific vulnerability to depression and anxiety. To address this, we examined female mice across the estrous cycle, in early diestrus (low-estrogen) and proestrus (high-estrogen), together with males. Females in diestrus exhibit higher anxiety levels compared to proestrus females and males, implying that a physiological drop in estrogen increases anxiety risk**.** To address the underlying mechanism, we assessed the effects of the estrous cycle and sex on chromatin organization (ATAC-seq) and gene expression (RNA-seq) in FACS-purified neuronal nuclei from the ventral hippocampus, an area strongly implicated in anxiety. We show that neuronal chromatin organization significantly fluctuates with the estrous cycle and differs between sexes. We find changes in chromatin organization associated with the transcriptional activity of genes important for neuronal excitability, neurotransmission, synapse formation, and anxiety behavior. The expression of chromatin regulators also varies with the estrous cycle, underscoring the importance of dynamic chromatin regulation for female brain function. Our findings implicate an estrogen-responsive, immediate early gene product, Egr1, as part of the signaling mechanism mediating estrous cycle-dependent chromatin and transcriptional changes. This study reveals extreme dynamism and sex-specificity of the neuronal epigenome, and facilitates the development of sex-specific treatments for neuropsychiatric disorders such as anxiety and depression.

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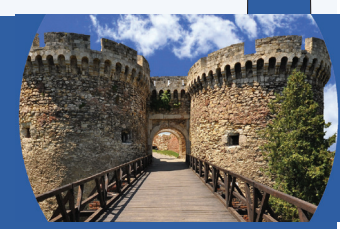

Saturday, July 13, 2019

8:30–10:10

Room Pacific

SYMPOSIUM 30

NEUROEPIGENETICS AND BRAIN DISORDERS

Organizers: Marija Kundakovic (New York, NY, USA)

RESILIENCE AND VULNERABILITY IN THE RESPONSE TO ACUTE AND CHRONIC STRESS: A ROLE FOR MICRORNAS

Maurizio Popoli

Laboratory of Neuropsychopharmacology and Functional Neurogenomics - Department of Pharmacological and Biomolecular Sciences, University of Milano,Milano, Italy

maurizio.popoli@unimi.it

Stressful events represent a major risk factor for stress-related neuropsychiatric disorders (1). Recently, we dissected the destabilizing effects of both acute/chronic stress in prefrontal cortex (PFC) and hippocampus (HPC), respectively. The chronic mild stress protocol (CMS, 5 weeks) and the footshock inescapable stress protocol (FS, 40 min) were used. CMS rats were deemed resilient (CMS-R) or vulnerable (CMS-V) for behavior (anhedonia) by using sucrose preference. Glutamate release from hippocampal synaptosomes was selectively reduced in CMS-vulnerable (CMS-V) but not CMS–resilient (CMS-R) rats. Significant reduction in expression of BDNF was found in all CMS rats. Reduced dendritic trafficking of BDNF mRNA and atrophy of apical dendrites was found in CA3 of CMS-V only. In CMS-V rats, sub-anesthetic ketamine (10 mg/kg) treatment in 24 h completely restored anhedonic behavior and all cellular/molecular changes, with the only exception of BDNF expression (2). At molecular level, we measured the expression of a set of microRNAs. We found that the levels of miR-9, a miRNA particularly abundant in brain, previously found to induce changes in neuronal morphology, were selectively decreased in the HPC of CMS-V, while ketamine restored the reduction. Using in situ hybridizations on HPC sections, we highlighted a region-specific pattern of reduced expression, and alterations in dendritic trafficking, of miR-9. Furthermore, we tested its effect on neuronal morphology by overexpression/down-regulation in neuronal cultures. Acute FS-stress rapidly enhanced glutamate release in PFC, an effect sustained for at least 24 hours (3). Unexpectedly, significant atrophy of apical dendrites was observed already at 24 h, and prolonged for at least 14 days. A single ketamine administration blocked the acute stress-induced enhancement of glutamate release when administered 24 or 72 h before, or 6 h after FS-stress. We measured the expression of the same set of miRNAs as after CMS and found 4 miRNAS reduced after acute stress. Two of them were among those reduced by CMS. Our results suggest that alterations in miRNA expression and trafficking (particularly miR-9) are involved both in mechanisms of stress resilience and in the fast antidepressant effect of ketamine.

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SYMPOSIUM 30

NEUROEPIGENETICS AND BRAIN DISORDERS

Organizers: Marija Kundakovic (New York, NY, USA)

GLUTAMATERGIC DYSREGULATION IN BIPOLAR DISORDER: GENETIC OR EPIGENETIC PROBLEM?

Marin Veldic

Mayo Clinic, Rochester, Minnesota, USA

veldic.marin@mayo.edu

Bipolar disorder (BD) is characterized by recurrent episodes of elevated mood and depression, interspersed with normal mood periods, often accompanied by drastic changes in energy levels that can severely affect the individual's daily life. There is increasing recognition that glutamatergic dysregulation is implicated in the neurobiology of mood disorders. While the etiology of BD remains uncertain, its high heritability supports the involvement of genetic and heritable epigenetic factors. In our presentation we will show evidence for both, genetic and epigenetic, pathophysiology. Two SNPs (rs3812778 and rs3829280), in perfect linkage disequilibrium, of the excitatory amino acid transporter 2 gene *SLC1A2,* were associated with elevated anterior cingulate glutamate in minor allele carriers ($p<0.001$) and had a significantly higher risk for rapid cycling (p=0.006). To study BD-associated DNA methylomic we extracted genomic DNA from the postmortem tissues of Brodmann Area (BA) 9 and BA38 from 20 BD, ten major depression (MDD), and ten control matched subjects. Genome-wide methylation levels were measured using the 850K Illumina MethylationEPIC BeadChip. We detected striking number of between brain region differentially methylated positions. Pathways enriched in the BD-only list suggested glutamatergic dysregulation and more impacts on synaptogenesis and synaptic plasticity. We further detected group-specific between-brain-region gene expression differences in *ODC1, CALY, GALNT2,* and *GABRD.* In summary, the methylation differences between various brain regions may provide molecular targets for further investigations of genetic and environmental vulnerabilities associated with mood disorders and suggest directions of future development of individualized treatment strategies.

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Room Atlantic 1

Symposium 31

Autophagy regulation and its role in neuronal function, survival, and death

Organizers: Vladimir Trajkovic (Belgrade, RS)

REGULATION AND ROLES OF AUTOPHAGY IN THE CENTRAL NERVOUS SYSTEM

Nektarios Tavernarakis

Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas; Medical School, University of Crete, Heraklion, Crete, Greece

tavernarakis@imbb.forth.gr

Autophagy is crucial for neuronal integrity. Loss of key autophagic components leads to progressive neurodegeneration and structural defects in neuronal synapses. However, the molecular mechanisms regulating autophagy in the brain remain elusive. Similarly, while it is widely accepted that protein turnover is required for synaptic plasticity, the contribution of autophagy to the degradation of synaptic proteins is unknown. We find that BDNF signaling via the tropomyosin receptor kinase B (TrkB) and the phosphatidylinositol-3 kinase (PI3K)/Akt pathway suppresses autophagy in vivo. Autophagy is differentially regulated by fasting in different brain regions. Suppression of autophagy is required for BDNF-induced synaptic plasticity and for memory enhancement, under conditions of nutritional stress. BDNF signaling suppresses autophagy in the forebrain of adult mice. Indeed, BDNF ablation in the neural lineage causes uncontrolled increase in autophagy. In turn, increased autophagy mediates the synaptic defects caused by BDNF deficiency. Thus, fasting suppresses autophagy in regions of the mouse forebrain, thereby promoting synaptic remodeling and memory through a BDNF-regulated mechanism. We identify three key remodelers of postsynaptic densities as cargo of autophagy. Our results establish autophagy as a pivotal component of BDNF signaling, which is essential for BDNF-induced synaptic plasticity. This molecular mechanism underlies behavioral adaptations that increase fitness in times of scarcity.

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SYMPOSIUM 31

AUTOPHAGY REGULATION AND ITS ROLE IN NEURONAL FUNCTION, SURVIVAL, AND DEATH

Organizers: Vladimir Trajkovic (Belgrade, RS)

AUTOPHAGY AS A MECHANISM OF OXIDATIVE STRESS RESPONSE

Viktor Korolchuk

Institute for Cell and Molecular Biosciences, Newcastle University, Newcastle, United Kingdom

viktor.korolchuk@ncl.ac.uk

Autophagy is a cornerstone of cellular physiology and is an attractive target for interventions that could help prevent age-related decline such as deregulation of protein homeostasis, genomic instability and tissue degeneration. Ageing and age-related diseases are also associated with increased levels of oxidative stress and autophagy has been shown to act as a stress-response pathway and can become activated in response to increased levels of reactive oxygen species (ROS). However, the mechanisms linking redox imbalance and autophagy activation remain poorly understood. We have recently discovered that several receptor proteins that mediate selective autophagy pathways can act as ROS sensors. We began unraveling the mechanisms by which receptor oxidation promotes their oligomerisation and enhances autophagosome formation as well as cell survival in conditions of oxidative stress. By focusing on two autophagy receptors, p62 and NDP52, this talk will illustrate our efforts to establish the role of receptor oxidation as a mechanism coordinating the levels of cellular damage with pro-survival autophagy. Importantly, interventions which stimulate autophagy receptor oligomerisation may be a promising novel approach to induce autophagy in a specific manner. We are working towards designing small molecules that could be used to "activate" receptor proteins and promote selective autophagy pathways.

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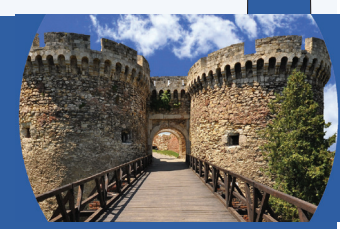

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SYMPOSIUM 31

AUTOPHAGY REGULATION AND ITS ROLE IN NEURONAL FUNCTION, SURVIVAL, AND DEATH

Organizers: Vladimir Trajkovic (Belgrade, RS)

TARGETING THE DARK SIDE OF AUTOPHAGY TO PROTECT AGAINST NEURONAL DEATH: EVIDENCES FROM NEONATAL CEREBRAL HYPOXIA-ISCHEMIA

Julien Puyal

Department of Fundamental Neurosciences, University of Lausanne, Lausanne, Switzerland

JulienPierre.Puyal@unil.ch

The deregulation of (macro) autophagy, a physiological intracellular process of lysosomal degradation, appears to play a dual role in different neurological conditions, since autophagy is reduced and impaired in neurodegenerative diseases but excessively activated in acute brain disorders such as perinatal cerebral hypoxia-ischemia. My presentation will focus on the involvement of autophagy in the pathophysiology of perinatal cerebral hypoxia-ischemia. Autophagy is enhanced in hypoxic-ischemic dying neurons both in vitro and in rat models of perinatal brain injury. Autophagy was shown to be deleterious by, depending the conditions, mediating apoptosis or being a death-promoting pathway by itself (independent of apoptosis and necrosis). Finally, and more clinically relevant, high neuronal autophagic activity is also present in dying neurons (thalamus and basal ganglia) in autoptic brains of human asphyxiated babies with severe hypoxic-ischemic encephalopathy (HIE). Altogether, these results cast light on a new mechanistic pathway in the pathophysiology of HIE and suggest that experimental neuroprotective strategies targeting autophagy should be considered for the development of future therapeutic approaches for neonatal asphyxia.

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SYMPOSIUM 31

AUTOPHAGY REGULATION AND ITS ROLE IN NEURONAL FUNCTION, SURVIVAL, AND DEATH

Organizers: Vladimir Trajkovic (Belgrade, RS)

AUTOPHAGY REGULATION AND ITS ROLE IN GLUTAMATE EXCITOTOXICITY DURING NUTRIENT STRESS

Ljubica Vucicevic[1], Maja Misirkic[1], Darko Ciric[2], Tamara Martinovic[2], Maja Jovanovic[3], Aleksandra Isakovic[3], Ivanka Markovic[3], Nevena Zogovic[1], Mark Foretz[5], Yoana Rabanal-Ruiz[6], Viktor I. Korolchuk[6], and Vladimir Trajkovic[7]

1Institute for Biological Research "Sinisa Stankovic, University of Belgrade, Belgrade, Serbia;
2Institute of Histology and Embryology, School of Medicine, University of Belgrade, Belgrade, Serbia;
3Institute of Medical and Clinical Biochemistry, School of Medicine, University of Belgrade, Belgrade, Serbia;
4Department of Neurophysiology, Institute for Biological Research "Sinisa Stankovic", University of Belgrade, Belgrade, Serbia;
5INSERM, U1016, Institut Cochin, Paris, France;
CNRS, UMR8104, Paris, France;
Université Paris Descartes, Sorbonne Paris Cité, France;
6Institute for Cell and Molecular Biosciences, Newcastle University, Newcastle upon Tyne, UK;
7Institute of Microbiology and Immunology, School of Medicine, University of Belgrade, Belgrade, Serbia

ljubicavucicevic@hotmail.com

We investigated the effect of excitotoxic glutamate on nutrient starvation-induced autophagy, a process of lysosome-mediated degradation of cellular macromolecules and organelles. Incubation of SH-SY5Y human neuroblastoma cell line in glucose/amino acid/serum-free Hank Balanced Salt solution synergized with glutamate in causing energy stress and excitotoxic necrosis. Glutamate inhibited starvation-induced autophagy, as demonstrated by decreased intracellular acidification, lower LC3 punctuation, reduced conversion of LC3-I to LC3-II, reduced expression of autophagy activators beclin-1 and ATG5, increased levels of the selective autophagic target NBR1, and decline in the number of autophagic vesicles observed by transmission electron microscopy. NMDA antagonist memantine restored LC3B-II accumulation in starved cells exposed to glutamate, indicating that glutamate exerts its inhibitory role on autophagy by activating NMDA receptors. The modulation of mTOR, the negative regulator of autophagy, was not responsible for glutamate-mediated autophagy inhibition during starvation. On the other hand, glutamate downregulated starvation-induced activation of the intracellular energy sensor AMP-activated protein kinase (AMPK). This was associated with reduced mRNA expression of autophagy transcription factors FOXO3 and ATF4, as well as molecules involved in autophagy process (ULK1, ATG13, FIP200, ATG14, beclin-1, ATG5, ATG12, SQSTM1). The ability of glutamate to repress transcription of autophagy genes in starved cells was partly mediated by AMPK downregulation. Genetic or pharmacological AMPK activation by AMPK overexpression or metformin, as well as genetic or pharmacological autophagy induction by TFEB overexpression or lithium chloride, rescued cells from glutamate-mediated excitoxicity. These data indicate that transcriptional inhibition of AMPK-dependent autophagy is involved in glutamate-mediated excitotoxicity during nutrient deprivation *in vitro*.

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Room Atlantic 2

SYMPOSIUM 32

DISTRIBUTED NEURONAL CIRCUITS OF FEAR

Organizers: Francesco Ferraguti (Innsbruck, AT) and Enrica Paradiso (Innsbruck, AT)

CIRCUIT MECHANISMS OF THREAT MEMORY IN AUDITORY CORTEX

Tamas Dalmay[1], Elisabeth Abs[1], Rogier B. Poorthuis[1], Sebastian Onasch[1], Yave R. Lozano[2], Philip Tovote[2], Julijana Gjorgjieva[1,3], Johannes J. Letzkus[1]

1Max Planck Institute for Brain Research, Frankfurt, Germany;
2University Hospital Würzburg, Institute of Clinical Neurobiology, Würzburg, Germany;
3School of Life Sciences, Technical University of Munich, Freising, Germany

johannes.letzkus@brain.mpg.de

Memory for cues associated with threat is critical for survival, and a leading model for elucidating how sensory information is linked to adaptive behavior by learning. While the brain-wide circuits mediating auditory threat memory have been intensely investigated, it remains unclear whether auditory cortex is critically involved. Here, we use a combination of optogenetic activity manipulations in defined cortical areas and output pathways, viral tracing, pathway-specific *in vivo* 2-photon calcium imaging and computational analyses of population plasticity to reveal that auditory cortex is selectively required for memory to complex stimuli. Conversely, stimulus processing in adjacent temporal association cortex is vital for all forms of cued threat memory. This medio-temporal impact gradient is paralleled by the organization of projections to the lateral amygdala, which govern threat memory expression through a balanced form of population plasticity selectively supporting the discrimination of significant sensory stimuli. Neocortical processing thus plays a critical role for cued threat memory.

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SYMPOSIUM 32

DISTRIBUTED NEURONAL CIRCUITS OF FEAR

Organizers: Francesco Ferraguti (Innsbruck, AT) and Enrica Paradiso (Innsbruck, AT)

STATE-DEPENDENT REGULATION OF FEAR EXTINCTION LEARNING BY INSULAR CORTICAL CIRCUITS

Klein, Alexandra[1]; Herry, Cyril[2]; Gogolla, Nadine[1]

1Max Planck Institute of Neurobiology, Circuits for Emotion Research Group, Martinsried, Germany;
2Université de Bordeaux, Neurocentre Magendie, U862, Bordeaux, France

ngogolla@neuro.mpg.de

Aim: Fear and anxiety elicit adaptive behavioral responses to avoid or reduce harm and thus ensure survival. However, fear is maladaptive when it persists in the absence of direct threat. Fear regulation mechanisms enable an organism to inhibit fear responses as circumstances change from threatening to safe. While the insular cortex is increasingly recognized as an intricate part of a wider neuronal network regulating fear and anxiety, the underlying neuronal computations remain elusive. Here, we aimed at investigating whether and how the posterior insular cortex (pIC) affects fear extinction learning.

Methods: We used fiber photometry and electrophysiological single-unit recordings in the pIC as well as optogenetic circuit manipulations throughout the course of fear conditioning and extinction learning to elucidate the processing of conditioned and unconditioned stimuli in the pIC as well as its contribution to fear extinction learning.

Results: Using fiber photometry and electrophysiological single-unit recordings in the pIC, we found state-dependent processing of fear-eliciting cues. Interestingly, CS+ -evoked pIC activities were correlated with fear-levels specifically during phases of learning, when the associative meaning of the CS+ changes. Optogenetic silencing of the pIC during extinction learning revealed surprising, bidirectional effects: while pIC inhibition facilitated extinction learning in animals expressing low fear levels during recall, the same circuit manipulation impaired fear extinction learning in animals expressing high levels of fear.

Conclusions: Our data suggest that the pIC may gate fear extinction efficacy dependent on the internal fear state of the animal.

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Symposium 32

Distributed Neuronal Circuits of Fear

Organizers: Francesco Ferraguti (Innsbruck, AT) and Enrica Paradiso (Innsbruck, AT)

SYNAPTIC CIRCUITS OF THE EXTENDED AMYGDALA AND THEIR ROLE IN SUSTAINED FEAR

Lange MD

Institut of Physiology I, WWU Münster, Münster, Germany

m.lange@uni-muenster.de

The response to a threat can shift from a rapid phasic state of fear to a more sustained anxious apprehension, particularly in face of diffuse cues with unpredictable environmental contingencies. Unpredictability, in turn, is considered as an important variable contributing to anxiety disorders. We have recently demonstrated that cannabinoid type 1 receptors (CB1) on distinct amygdala inputs to neurons in the anterolateral BNST (alBNST) are causal for a shift to sustained fear. However, subpopulations of neurons driving the CB1-effect remain elusive. To identify specific cell populations critically involved in regulating the fear profile we combined retrograde tracer studies with immunohistochemistry, optogenetic and electrophysiological approaches. Further, CRH-cre mice were crossed with floxed-STOP-CB1 mice and tested in a Pavlovian-conditioning-paradigm with unpredictable CS-US occurrence concerning CB1-CRH interaction. Behavioral results indicated specific rescue of CB1-receptors in CRH neurons resulting in reconstitution of the sustained fear phenotype. First evidence obtained from optogenetic and electrophysiological approaches corroborated these findings in showing that projections from centrolateral amygdala (CeL) to alBNST expressed CRH in a large portion. Further, CRH-positive inputs from CeL to alBNST seem to reside CB1-receptors. These CB1-receptors seem to be activated via 2-AG which regiments the CRH-effect thereby. The results suggest a causal role for 2-AG-CRH interaction in circuits of the extended amygdala. It seems to be crucial for the development of a sustained state of anxious apprehension as a response to prior experienced unpredictable environmental influences.

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Room Atlantic 2

Symposium 32

Distributed Neuronal Circuits of Fear

Organizers: Francesco Ferraguti (Innsbruck, AT) and Enrica Paradiso (Innsbruck, AT)

AMYGDALA MICROCIRCUITS FOR AVERSIVE LEARNING

Enrica Paradiso[1,2], Sabine Krabbe[1], Simon D'Aquin[1,3], Yael Bitterman[1], Chun Xu[1,4], Keisuke Yonehara[1,5], Milica Markovic[1,3], Jan Gründemann[1,6], Francesco Ferraguti[2], Andreas Lüthi[1,3]

1Friedrich Miescher Institute for Biomedical Research, 4058 Basel, Switzerland;
2Department of Pharmacology, Medical University of Innsbruck, Innsbruck, Austria;
3University of Basel, Basel, Switzerland;
4Present Address: Institute of Neuroscience, Chinese Academy of Sciences, Shanghai, China;
5Present Address: Danish Research Institute of Translational Neuroscience – DANDRITE, Nordic-EMBL Partnership for Molecular Medicine, Aarhus University, Department of Biomedicine, Aarhus C, Denmark;
6Present Address: Department of Biomedicine, University of Basel, Basel, Switzerland

enrica.paradiso@i-med.ac.at

The basolateral amygdala (BLA) is a cortical-like structure known to be involved in highly adaptive forms of emotional learning necessary for survival. Local plasticity of excitatory projection neurons (PNs) in the BLA is considered to be crucial for fear learning. BLA GABAergic interneurons tightly regulate PNs excitability, however, little is known about their contribution to fear memory formation. BLA interneurons are highly heterogenous in their neurochemical, physiological and anatomical features. In particular, whereas most subtypes of interneuron target distinct plasma membrane domains of PNs, other subtypes selectively innervate other interneurons. Using fear conditioning as a model for associative learning, we found that salient stimuli cause learning by recruiting a local BLA microcircuit consisting of precisely connected subtypes of inhibitory interneurons. By means of calcium imaging and optogenetics in freely behaving mice we demonstrate that vasoactive intestinal polypeptide (VIP)-expressing interneurons in the BLA are strongly activated by aversive events during associative fear learning and that they provide an instructive signal necessary for associative learning. Notably, VIP BLA interneuron responses are plastic and shift from instructive to predictive cues upon memory formation. Furthermore, using a mono-trans-synaptic retrograde tracing approach, we identified direct inputs to VIP BLA interneurons from brain areas involved in sensory-emotional processing and delivery of aversive information. Therefore, adaptive gating by VIP interneurons might be a general operational principle that allows to discriminate important from irrelevant sensory stimuli and to facilitate stimulus-associations to ensure appropriate behavioral adaptations to salient events.

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Room Mediterranean

SYMPOSIUM 33

COGNITIVE NEUROSCIENCE AND ADDICTIVE BEHAVIORS

Organizers: Mohammad Taghi Joghataei (Tehran, IR)

ADDICTION AS A BRAIN DISORDER

Mohammad Taghi Joghataei

Neuroscience Research Center, Iran University of Medical Sciences, Tehran, Iran;

joghataei@tums.ac.ir

The negative stigma to look at addiction as a purely bad choice, habit, moral failing, lack of self-control, a social and criminal problem has changed during the last two decades. The research findings have emphasized on the neurobiology of the disorder to consider it as a brain disorder which makes the drug abuse some how a medically treatable disorder. Studies have shown that substance use creates long-lasting impairments to structure and functions of the brain, which makes it painfully hard to kick. In this talk, a comprehensive review of recent findings on desensitization of the brain's reward circuit and its link to impairment of the executive functions like decision-making, impulse control and self-regulation are provided.

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SYMPOSIUM 33

COGNITIVE NEUROSCIENCE AND ADDICTIVE BEHAVIORS

Organizers: Mohammad Taghi Joghataei (Tehran, IR)

STRESS, COGNITION AND ADDICTIVE BEHAVIORS

Abbas Haghparast

Neuroscience Research Center, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

haghparast@yahoo.com

Stress, as one of the common problems in the current century, affects different brain structures involved in cognitive behaviors such as decision-making, learning and memory, attention, reward, and etc. There are numerous evidences indicating that stress influences performance of several cognitive tests like decision making and impairs the operant tasks involving effort and cognitive flexibility. Besides, stress is a key risk factor in the development of addiction and relapse. Stress affects reward pathways to potentiate motivation and consumption of addictive drugs. It has been shown that the dopaminergic system in reward circuitry has a critical role in relapse to drugs of abuse, induced by exposure to a stressor. There is convincing evidence that early and adult stressful life events are risk factors for the development of addiction and serve as cues that trigger induction of addiction and relapse. Previous findings have shown the involvement of glucocorticoid receptors in the amygdala in stress-induced reinstatement of the methamphetamine-extinguished animals. Forced swim stress also affects the acquisition of morphine-induced conditioned place preference and food deprivation stress induced the reinstatement to morphine. Therefore, it can be suggested that treatment of addiction and drug dependency should involve cognitive and pharmacological approaches that enhance resilience in risk individuals. It is also imperative to elucidate the mechanisms underlying the interactions between stress and drugs of abuse, as an understanding of this may help in the development of novel and more effective therapeutic approaches to block the clinical manifestations of drug addiction.

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SYMPOSIUM 33

COGNITIVE NEUROSCIENCE AND ADDICTIVE BEHAVIORS

Organizers: Mohammad Taghi Joghataei (Tehran, IR)

FUNCTIONAL AND STRUCTURAL CHANGES ASSOCIATED WITH METHAMPHETAMINE ABUSE

Reza Khosrowabadi

Institute for Cognitive and Beain Science, Shahid Beheshti University, Tehran, Iran

r_khosroabadi@sbu.ac.ir

Methamphetamine (MA) is a potent psychostimulant drug whose abuse has become a global epidemic in recent years. In this talk, epidemiology and clinical pharmacology of methamphetamine dependence is briefly discussed. Subsequently, relevant animal models of methamphetamine dependence are reviewed and possible mechanisms of methamphetamine-induced neurotoxicity are discussed. Then, a critical review of functional and structural neuroimaging studies in human MA abusers are provided. After, findings of neuroimaging studies based on positron emission tomography, functional and structural magnetic resonance imaging are explained. Finally, a new study on MA effects on active users considering neuronal cell death mechanisms including apoptosis, autophagia, and necroptosis is presented. The results showed activations of right inferior and middle temporal gyri significantly differ in MA addicts versus the controls. In addition, white matter volumes of right superior temporal gyrus, left temporal lobe, right frontal lobe and left medial frontal gyrus were increased in MA addicts. Nevertheless, molecular analyses detected no significant differences in the plasma levels of the studied proteins as well as miRNAs of MA addicts; despite higher levels of MBP, S100B and TNFα were observed in MA abusers. Theese findings points to induced physiological and structural changes in MA addicts. However, considering no significant differences at the plasma proteins and miRNAs, not an extensive neuronal death is proposed in MA abusers.

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SYMPOSIUM 33

COGNITIVE NEUROSCIENCE AND ADDICTIVE BEHAVIORS

Organizers: Mohammad Taghi Joghataei (Tehran, IR)

THE INFLUENCE OF PROPOFOL ON MOOD AND MEMORY IN ADOLESCENCE – FINDINGS IN ANIMAL MODEL

Željko Pavković, Milica Potrebić, Selma Kanazir, Vesna Pešić

Department of Neurobiology, Institute for Biological Research "Siniša Stanković", University of Belgrade, Belgrade, Serbia

vesnav@ibiss.bg.ac.rs

Propofol gains much attention during recent years because, in addition to its pharmacological advantages over other anesthetics, it has addictive potential. Considering a wide usage of propofol in pediatric anesthesia, the question that deserves to be comprehensively answered is what neuropsychological effects of a single propofol anesthesia exposure (PAE), representing the typical medical usage of propofol, could be expected in adolescence as a period of increased vulnerability to drugs. To the best of our knowledge, this issue has been addressed only in our research, which provides basing findings using peripubertal rats as the rodent model of periadolescence. Our findings indicate that in peripubertal rats PAE produces i) transient changes in the expression/phosphorylation of biochemical markers already described as essential in the molecular pathways underlying drug addiction and development of behavioral sensitization, ii) affects memory retrieval and acquisition of new learning in the spatial and nonspatial nonaversive learning tasks, iii) affects motivation in goal directed actions, promotes hedonic response to novel/intense stimuli and risk-taking/sensation-seeking. Indications that PAE produces atypical behaviors in subjects that pass through a transitional stage with already recognized natural risk tendencies and synaptic changes in systems implicated in motivation/reward/addiction may have clinical implications, emphasizing the necessity of clinical research focused on this concept.

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Room Baltic

Symposium 34

On the crossroad of epilepsy and Alzheimer's disease: from genes to behavior

Organizers: Maria Angela Sortino (Catania, IT) and Olivera Stanojlovic (Belgrade, RS)

EXPERIMENTAL MODELS OF EPILEPSIES: MECHANISTIC APPROACH TO HYPEREXCITABILITY

Olivera Stanojlović

Laboratory of Neurophysiology, Institute of Medical Physiology "Richard Burian", Faculty of Medicine, Belgrade, Serbia

ostanoj@gmail.com

Millions of people worldwide suffer of epilepsy which is a chronic neurological condition characterized by recurrent seizures. Electrical and behavioral combination are seizures events that are able to induce molecular, chemical and of course functional alterations. Neurophysiological similarities and differences between the model and the human equivalent were recognized. Seizure models are unique opportunity to study complex mechanisms underlying epileptogenesis and seizure generation, as well as for identifying a truly novel ant seizure drug or potential therapeutic agents. The quest for seizure mechanisms can provide insights into overall brain functions and consciousness that is the reason why animal models of epilepsy will continue to promote the progress of neurophysiology research. On the other hand research has focused on elucidating the mechanisms of epileptogenesis so as to identify specific targets and to preventing epilepsy before seizures emerge. Rodents with spontaneous recurrent seizures have been generated by using chemoconvulsants (in both immature and mature brain), in our laboratory we used pilocarpine, metaphit, homocysteine, imipemen-cylastatin, lindane and and so on, for brain synchronization and excessive discharge of neurons. Studies of hyperexcitability and epileptogenesis/ictogenesis are related to ion channels, GABA-ergic neurotransmission, NMDA receptor complex, neuroinflamation, gaseous neurotransmitters, but also other numerous mechanisms such as dysregulation of molecular signaling pathways, cell type-specific dysfunction or pathology of discrete circuit elements. This lecture will try to light the shadow on hyperexcitability mechanisms.

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Room Baltic

Symposium 34

On the crossroad of epilepsy and Alzheimer's disease: from genes to behavior

Organizers: Maria Angela Sortino (Catania, IT) and Olivera Stanojlovic (Belgrade, RS)

MOLECULAR MECHANISMS IN ALZHEIMER'S DISEASE: IMPLICATIONS FOR COMORBIDITIES

Sara Merlo; Simona Federica Spampinato; Grazia Ilaria Caruso; Maria Angela Sortino

Department of Biomedical and Biotechnological Sciences, Section of Pharmacology, University of Catania, Catania, Italy

sara_merlo@hotmail.com

Alzheimer's Disease (AD) is a progressive neurodegenerative condition, leading to memory loss and severe cognitive disabilities. An early onset form of AD is linked to selective genetic mutations, while a more common late-onset sporadic form affects the elderly over 65. Both are characterized by exceeding accumulation of beta amyloid protein (Abeta) and phosphorylated tau protein (p-tau), resulting in brain deposition of Abeta plaques and p-tau tangles. Abeta triggers multiple and concomitant cellular events, not only directly on neurons, but also targeting the glial component. Glial activation impacts neuronal susceptibility to toxic insults, with different outcomes during progressive stages of disease development. While inflammatory responses start as an initial defensive reaction, they can become chronic and contribute to disease worsening. Sustained neuroinflammation in AD is a pathogenic mechanism that is shared with other neurological or systemic diseases, such as multiple sclerosis, Parkinson's Disease or peripheral inflammation, implicating an important role for comorbidities in the progression rate of the pathology. In this regard, epilepsy and AD have recently emerged as important comorbid conditions that can reciprocally affect clinical features.

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SODIUM PUMP AND ITS ROLE AS SIGNAL TRANSDUCER IN BRAIN DISORDERS

Ekaterina Lopatina[1,3], Maria Sokolova[2], Valentina Penniyaynen[3],Anna Kipenko[1], Natalia Pasatetskaya [3,4], Artur Gavrichenko[1], Alexey Lopatin[1]

1Pavlov First St. Petersburg State Medical University St. Petersburg, Russia;
2North-West State Medical University named after I.I. Mechnikov, St. Petersburg, Russia;
3 Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia;
4Almazov National Medical Research Centre, St. Petersburg, Russia

evlopatina@yandex.ru

Spinal muscle atrophy (SMA) of type I and II is an autosomal-recessive disease. The disease is manifested in weakness of proximal muscles, pareses, respiratory disturbance and early death. SMA is an incurable disease. In our preliminary investigation was found high concentrations of neurotrophins in blood patients with SMA. This fact led us to the idea of studying receptor-based mechanisms of influencing motoneurons to activate the processes of reinnervation. We hypothesized the participation non pumping function Na,K-ATPase, in this process. The subject of the study: patients undergoing clinical and neurological examination, and the blood serum of the patients. 18 patients from 1 to 12 years old with the confirmed molecular-genetic analysis diagnosis of SMA type I and type II were examined. The control group consist from 30 healthy children. The collection of venous blood, its storage and handling for serum isolation was performed. In organotypic tissue culture in the presence of serum of patients with SMA of type I and II, it was found neuritis -inhibiting effect of serum. The neurotoxic effect of plasma was not observed in the presence comenic acide in the culture medium. Thus, it can be stated that the modulation of the non pumping function of the Na,K-ATPase is the trigger of the mechanisms of the counteracting the toxic effect (neurite-inhibiting growth) of plasma of SMA type I and II patients.

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ON THE CROSSROAD OF EPILEPSY AND ALZHEIMER'S DISEASE: FROM GENES TO BEHAVIOR

Organizers: Maria Angela Sortino (Catania, IT) and Olivera Stanojlovic (Belgrade, RS)

HIPPOCAMPAL NEUROPATHOLOGY IN BRAIN DISORDERS: THE ROLE OF GENETIC FACTORS IN EPILEPSY AND ALZHEIMER'S DISEASE

Yavuz Dodurga

Pamukkale University, Medical Faculty, Department of Medical Biology and Genetics, Denizli Turkey

yavuzdodurga@gmail.com

Alzheimer's disease (AD) is a clinically heterogeneous neurodegenerative disease with a strong genetic component. Epilepsy is one of the most common severe neurological disorders, affecting more than 50 million people worldwide. Understanding the etiology of AD and epilepsy can be beneficial for the diagnosis and intervention of this disease. Genetics plays a vital role in the pathogenesis of these diseases. Several genes have been associated with AD and epilepsy risk for decades. The recent technological advances that allow for the analysis of millions of genetic changes in thousands of subjects that we have been able to advance our understanding of the genetic complexity of AD and epilepsy susceptibility. Research methods in genetics such as the linkage analysis, study of candidate genes, genome-wide association study (GWAS), and next-generation sequencing (NGS) technology help us map the genetic information in AD and epilepsy, which can not only provide a new insight into the pathogenesis of AD and epilepsy but also be beneficial for early targeted intervention of AD and epilepsy. These studies have provided insights into the molecular pathways that are altered in AD and epilepsy pathogenesis, which have, in turn, provided insight into novel therapeutic targets and indicating the existence of novel genes on several chromosomes, epigenetic mechanisms, non-coding RNAs including miRNAs, lncRNA for further understanding of the molecular biology of AD and epilepsy. We will discuss all molecular mechanisms including genetic, epigenetic, miRNAs and lncRNAs.

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ASTROGLIAL CALCINEURIN REGULATES NEURONAL EXCITABILITY AND PROTEIN EXPRESSION

Dmitry Lim, Laura Tapella, Teresa Soda, Marcello Manfredi, Valeria Bortolotto, Lisa Mapelli, Heather Bondi, Luisa Ponzoni, Eleonora Conte, Simone Ummarino, Alessio Stevano, Chiara Verpelli, Mariagrazia Grilli, Mariaelvina Sala, Annalisa Di Ruscio, Emilio Marengo, Francesco Moccia, Egidio D'Angelo, Armando Genazzani

Department of Pharmaceutical Sciences, Università del Piemonte Orientale, Novara, Italy

dmitry.lim@uniupo.it

Astrocytes play fundamental homeostatic functions in the brain, yet they are involved in pathogenesis of brain diseases including Alzheimer's disease (AD) and epilepsy. Calcineurin (CaN) is a Ca^{2+}-sensitive phosphatase, which, in astrocytes, is known to trigger disease-associated neuroinflammation. Hypothesizing that astroglial CaN (Astro-CaN) may be involved in earlier phase of diseases, we have generated a mouse with CaN KO in GFAP-expressing astrocytes (Astro-CaN-KO). We observed that Astro-CaN-KO mice exhibit interictal spikes and by 12 month of age 50% of mice exhibit tonic-clonic seizures. Patch clamp recordings revealed that deletion of Astro-CaN converted high-frequency tonic neuronal firing into adaptive firing due to progressive reduction in K+ currents-mediated after-hyperpolarization, suggesting deficiency of astroglial Na+/K+ ATPase (NKA). We found reduced NKA activity in brain tissues and in astroglial (but not neuronal) cultures, as well as in WT samples treated with a CaN inhibitor. This suggests that Astro-CaN maintains neuronal excitability during intensive neuronal firing through activation of NKA in astrocytes. Searching for other targets of Astro-CaN we performed proteomic analysis of whole-tissue and synaptosomal fractions from Astro-CaN-KO. Strikingly, most of differentially expressed proteins were neuronal or neuron-enriched proteins. Gene ontology analysis revealed alteration in pre-synaptic compartment, ribosome, as well as in expression of mitochondrial and OXPHOS components, the latter being a part of pathways for AD, Parkinson and Huntington diseases. In conclusion, deletion of astroglial CaN produces features of both epilepsy and AD, suggesting that Astro-CaN activity alterations may represent a common element in brain diseases.

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SATELLITE SYMPOSIUM OF NEUROTOXICITY SOCIETY: NEW POTENTIAL THERAPEUTIC TARGETS IN CASE OF NEURODEGENERATIVE DISORDERS AND AGE-RELATED DEGENERATIVE PROCESSES

Organizers: Andrea Tamas (Pécs, HU) and Maria Trinidad Herrero (Murcia, ES)

CRITICAL ROLE OF TRPA1 RECEPTOR IN THE MOUSE BASAL FOREBRAIN CHOLINERGIC NEURONS IN VIVO

Éva Borbély[1,4], Maya Payrits[1,4], Klaudia Barabás[2,4], Angéla Kecskés[1,4] Balázs Gaszner[3], Viktória Kormos[1,4], Soma Godó[2,4], Dávid Ernszt[2,4], Ágnes Kemény[1], Ágnes Hunyady[1], József Kardos[6], István Ábrahám[2,4,5], Erika Pintér[1,4,5]

1Department of Pharmacology and Pharmacotherapy, Medical School, University of Pécs; Hungary;
2Department of Physiology, Medical School, University of Pécs; Hungary;
3Department of Anatomy, Medical School, University of Pécs; Hungary;
4Szentágothai Research Center, University of Pécs; Hungary;
5Centre for Neuroscience, University of Pécs, University of Pécs; Hungary;
6ELTE, Budapest; Hungary

erika.pinter@aok.pte.hu

Amyloid beta (Aβ1-42) accumulates in Alzheimer's disease (AD) that is toxic to the basal forebrain cholinergic (BFC) neurons in susbtantia innominata and nucleus basalis magnocellularis complex (SI-NBM). Transient Receptor Potential Ankyrin1 (TRPA1) receptors are expressed in nociceptive neurons and astrocytes, however their role in degenerative central nervous system diseases is unclear. We investigated TRPA1 receptors in Aβ1-42-induced neurotoxicity and aging. Expression of TRPA1 was examined by fluorescence immunohistochemistry and RNA.scope techniques. Aβ1-42 was injected into SI-NBM of wildtype (TRPA1+/+) and TRPA1 knockout (TRPA1-/-) mice. Cholinergic fibre loss was visualized by acetylcholinesterase, cholinergic cell loss with ChAT immunohistochemistry. Novel object recognition (NOR), radial arm maze (RAM) and Y-maze tests were used to investigate memory loss. Aβ1-42-injected WT mice showed significant cholinergic cell loss and cholinergic fiber loss, which was significantly attenuated in TRPA1-/- animals. In NOR and RAM tests significant memory loss was detected in Aβ1-42-injected TRPA1+/+ mice, but not in TRPA1-/- group. Old KO mice showed significantly milder memory loss, which could be seen as higher discrimination index in the NOR and less exploration time in the RAM. Our data demonstrate that TRPA1 might play a crucial role in neurotoxicity- and aging-induced dementia.

This study was supported by „The role of neuro-inflammation in neurodegeneration: from molecules to clinics" (EFOP-3.6.2-16-2017-00008) and the Hungarian Brain Research Program 2. 2017-1.2.1-NKP-2017-00002.

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Organizers: Andrea Tamas (Pécs, HU) and Maria Trinidad Herrero (Murcia, ES)

GUT INFLAMMATION EXACERBATES DOPAMINERGIC DEGENERATION AND PERPETUATES NEUROINFLAMMATION

María-Trinidad Herrero, Ana-Luisa Gil-Martínez, Lorena Cuenca, Cristina Estrada, Consuelo Sánchez-Rodrigo, Emiliano Fernández-Villalba

Clinical and Experimental Neuroscience Group (NiCE-IMIB), Institute for Aging Research, Biomedical Research Institute of Murcia (IMIB-Arrixaca), School of Medicine, University of Murcia, Murcia, Spain.

mtherrer@um.es

Different evidences point out that an inflammatory insult can affect the brain by the transmission of circulating cytokines and inflammatory mediators through two routes: systemic or neural. Some studies have focused on explaining how systemic inflammation is involved in the progression of the neuronal cell death in neurodegenerative disorders, like Parkinson's disease. In this work, through differentially-expressed genes (DEGs) analysis by microarray and bioinformatics approaches, we aimed to identify in depth the processes involved after the intoxication in the striatum of adult mice (16 three-months male C57BL/6J mice). We combined a dextran sodium sulfate (DSS)-induced ulcerative colitis experimental mice model with an acute 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxication. The animals were divided into four experimental groups based on the different treatments: i) control (n=4); i) MPTP (n=4); iii) DSS (n=4); iv) MPTP+DSS (n=4). The data obtained by microarray point out different mechanisms involved depending on the experimental groups. Thus, in animals intoxicated only with DSS, altered processes in the blood stand out; in MPTP mice, it was significantly express oxidative stress processes, and in MPTP+DSS group, it was mainly observed significant changes of programmed cell death. Interestingly, it was observed a significant synergistic negative effect of both toxins since the expression of DEGs related to balance cellular homeostasis (GO ID: 0042592) is not enough to prevent processes associated to cell death, significantly up-regulated (GO ID: 0012501; 0008219 or 0010941). Furthermore, these results are in accordance with the significant increase of the expression of genes related to immune system process (GO ID:0002376; 0031347 or 0006954) and oxidative stress (GO ID: 0055114 or 0006950). In conclusion, this study added new insights about how systemic inflammation, triggered after a specific insult in the colon, is involved in the progression of the degeneration in Parkinsonism.

This work was supported by the Spanish Ministry of Science and Innovation (FIS PI13 01293), Fundación Séneca (19540/PI/14)

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Organizers: Andrea Tamas (Pécs, HU) and Maria Trinidad Herrero (Murcia, ES)

EXAMINATION OF PACAP IN BLOOD SAMPLES OF PATIENTS WITH PARKINSON'S DISEASE

Andrea Tamas[1], Beata Polgar[2], Zalan Szanto[3], Adel Jungling[1], Norbert Kovacs[4], Istvan Balas[5], Endre Pal[4], Daniel Pham[1], Tunde Toth [1], Balazs Fazekas[1], Balazs Daniel Fulop[1], Attila Gyenesei[6], Dora Reglodi[1]

1Department of Anatomy, MTA-PTE PACAP Research Team, Centre for Neuroscience;
2Department of Medical Microbiology and Immunology;
3Department of Surgery;
4Department of Neurology;
5Department of Neurosurgery,6 Szentagothai Research Center, University of Pecs, Medical School, Hungary

andreatamassz@gmail.com

In the last few years numerous studies examined the presence and the changes of PACAP level in different human samples to show alterations in various physiological and pathological conditions. A recent study showed that plasma PACAP concentrations were significantly higher after acute spontaneous basal ganglia hemorrhage than in healthy controls. We have also found correlation between mortality and PACAP levels in severe traumatic brain injury. Han and coworkers demonstrated that PACAP levels were reduced in several brain areas and in postmortem CSF of Alzheimer's disease patients. The aim of the present study was to examine the PACAP in blood samples of patients with Parkinson's disease (PD) without treatment, with different levodopa treatment from different stages of PD based on Hoehn-Yahr scale and after deep brain stimulation. Sandwich-type ELISA (Mybiosource) was used to measure the PACAP38 level of plasma samples. Our preliminary results showed elevated PACAP38 levels in numerous plasma samples from patients with PD after deep brain stimulation. These results are similar to earlier experiments where elevated PACAP levels were found after basal ganglia and subarachnoid hemorrhage, after traumatic brain injury, in migraine and posttraumatic stress disorder. The neuroprotective and cytoprotective effect of PACAP is well known, therefore, the role of elevated endogenous PACAP level in these acute severe conditions could provide its protective function to restore the physiological conditions. Our further aim is to increase the number of examined patients to identify the prognostic and/or diagnostic biomarker value of PACAP-38 in case of Parkinson's disease.

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Organizers: Andrea Tamas (Pécs, HU) and Maria Trinidad Herrero (Murcia, ES)

CELL AND CONTEXT-SPECIFIC ACTIONS OF GLUCOCORTICOIDS IN PARKINSON'S DISEASE PATHOLOGY

Vyas S, Compagnion A-C, Maatouk L, Carrillo-de Sauvage M[1], Bemelmans A[1], Hirsch E.H[2], Giaume C[3], Herrero M-T[4], Michel P.P[2] Tronche F.

Gene Regulation and Adaptive Behavior laboratory, CNRS UMR 8246, INSERM U1130, Sorbonne Université, Paris, France;
1 Neurodegenerative Diseases Laboratory, MIRCen-CEA, Fontenay-aux-Roses, France;
2 ICM, INSERM UMRS 1127, CNRS UMR 7225, Sorbonne Université, Paris, France;
3CIRB, CNRS UMR 7241, INSERM U1150, Collège de France, Paris France;
4Clinical and Experimental Neuroscience group, School of Medicine, University of Murcia, Spain.

sheela.vyas@upmc.fr

Following environmental challenges such as stress or trauma, glucocorticoids (GCs) through glucocorticoid receptors (GRs) exert wide-ranging adaptive responses in many tissues, altering physiological and behavioral processes. GC-GR dysfunction is associated with many long-term diseases. Our work is focused on determining the contribution of GC-GR in pathophysiology of Parkinson's disease (PD). Both GCs (cortisol) and GR levels are altered in PD patients. Many studies including ours reported high levels of circulating cortisol levels; as well we found overall reduction of GR in substantia nigra and its upregulation in caudate putamen in PD post-mortem brains. Further work showed significant reduction in expression of GR in microglia and in astrocytes of substantia nigra brain samples from PD patients. Due to pleiotropic nature of GR signaling, we have generated mouse models in which GR can be conditionally inactivated in one cell type. Our work on its actions in microglia and astrocytes revealed its crucial role on the survival of dopaminergic neurons in MPTP and alpha-synuclein models of PD. However, it has specific actions in these cell types, for example in microglia it impacts significantly the innate immune functions whereas in astrocytes it acts not only to regulate inflammation through connexin hemichannels but is also involved in behavioral anomalies as observed in PD. Our work on its role in dopamine neurons revealed that in experimental Parkinsonism, GR can act to promote neuronal survival only when mice are given corticosterone treatment. Overall, our work highlights cell and context-specific actions of GCs and GR in PD pathology.

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Symposium 36

Transcriptional mechanisms: from neural fate decisions to curcuit assembly

Organizers: Nissim Ben-Arie (Jerusalem, IL) and Panagiotis Politis (Athens, GR)

THE ROLE OF LONG NON-CODING RNAS IN MAMMALIAN BRAIN DEVELOPMENT

Elpinicki Ninou, Maximilianos Elkouris, Nikos Malissovas, Daphne Antoniou, Panagiotis Politis

Center for Basic Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece

ppolitis@bioacademy.gr

Long non-coding RNAs (lncRNAs) constitute one of the most broad and diverse classes of cellular transcripts, playing key roles as regulatory molecules in many biological processes. Transcriptome analysis has identified a plethora of long non-coding RNAs (lncRNAs) expressed in the human brain and associated with neurodevelopmental and neurological diseases. Despite these observations, the functional roles of lncRNAs in mammalian brain development remain largely unknown. To this end, we have recently identified many lncRNAs highly expressed in neural cells during development. We have focused our efforts on lncRNA genes encompassing transcriptional units in close proximity to protein coding genes, encoding for transcription factors (TFs) with critical roles in brain development. We hypothesized that these lncRNAs may be implicated in the regulation of neighboring TF genes. In this study, we further investigated the functional role of a number of these lncRNAs-TF pairs in the differentiation of neural stem cells by *in vitro* and *in vivo* overexpression and knock-down studies. Our data suggest critical roles for these lncRNAs in neuronal differentiation and astrogliogenesis during brain development.

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TRANSCRIPTIONAL MECHANISMS: FROM NEURAL FATE DECISIONS TO CURCUIT ASSEMBLY

Organizers: Nissim Ben-Arie (Jerusalem, IL) and Panagiotis Politis (Athens, GR)

GEMININ SUPERFAMILY MEMBERS ARE CRITICAL SWITCH FOR ADULT NSC AND EPENDYMAL CELL SPECIFICATION

Maria-Eleni Lalioti[1], Konstantina Kaplani[1], Christina Kyrousi[1], Georgia Lokka[1], Theodore Georgomanolis[2], Akis Papantonis[2], Zoi Lygerou[3], Stavros Taraviras[1,*]

1Department of Physiology, Medical School, University of Patras, Greece, 2Center for Molecular Medicine Cologne, University and University Hospital of Cologne, Cologne, DE,3Department of General Biology, Medical School, University of Patras, Greece

taraviras@med.upatras.gr

A small number of heterogeneous populations of neural stem/progenitor cells (NSCs) is specified into distinct cell fates giving rise to central nervous system. Intrinsic and extrinsic signals govern mammalian NSCs fate specification and subsequent differentiation. It has been suggested that modification in chromatin architecture, epigenetic marks and transcription are crucial to determine fate commitment programs into a specific lineage. Our experimental evidence suggests that a novel family of proteins homologous to Geminin plays a key role on understanding how cell fates of adult NSCs and ependymal cells are established in the developing cortex and links these findings to the pathogenetic mechanisms of hydrocephalus.

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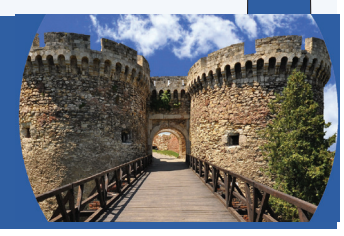

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Organizers: Nissim Ben-Arie (Jerusalem, IL) and Panagiotis Politis (Athens, GR)

VENTRAL SPINAL CORD DEVELOPMENT: FROM TRANSCRIPTIONAL REGULATION TO PATTERNING TO BEHAVIOR

Nissim Ben-Arie, Sophie Khazanov, Menucha Rubanowitz And Barak Weisman

Dept. of Cell & Developmental Biology, Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem, Israel

nbenarie@gmail.com

In amniotes, the entire central nervous system develops during embryogenesis from the neural tube. A combination of morphogenes induces rostro-caudal and dorso-ventral regionalization that give rise to the formation of various distinct structures. The dorso-ventral patterning is regulated by two organizing centers, the dorsal roof plate and the ventral floor plate. Despite significant progress made in deciphering the induction of the floor plate and the diversification of neural progenitors in the ventral spinal cord, the detailed mechanisms that regulate these processes are not fully understood. We found that the spatio-temporal expression profile of the transcription factor Nato3 coincides with fate determination and specification of floor plate cells, suggesting a possible role in establishing floor plate identity, and thereafter spinal cord patterning. To further enhance the effect of Nato3 deletion on CNS structure and function we attenuated Foxa2-Nato3 signaling pathway by generating bigenic mutant mice. The histological abnormalities as well as the behavioral outcome of the genetic manipulation will be described.

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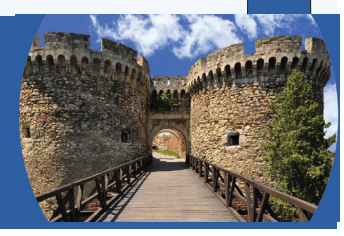

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DECIPHERING SPINAL NEURONAL CIRCUIT FOR REFINED LOCOMOTION AND WING FLAPPING IN CHICK - GENETIC TARGETING, FUNCTIONAL ORGANIZATION AND BEHAVIORAL ANALYSIS

Baruch Haimson, Reut Sudakevitz, Oren Meir and Avihu Klar

Department of Medical Neurobiology, IMRIC, the Hebrew University Medical School, Jerusalem, Israel

avihu@mail.huji.ac.il

Birds are bipedal organism that walk by leg alternation, and fly via synchronous wing flapping. In mice, the repulsive axon guidance molecule Ephrin-B3, serves as a midline barrier for axons of spinal excitatory commissural pre-motor interneurons. Mice null for *Ephrin-B3* hop by synchronous gait. We found that a midline-specific enhancer element of *Ephrin-B3* is missing in all birds. Secondary mutations have led to *Ephrin-B3* deletion in chick or **pseudogene** in songbirds. We report axonal decussation of excitatory pre-motor interneurons at the brachial, but not lumbar, dorsal spinal cord. To challenge the role of the *Ephrin-B3* deletion in the decussation of axons at the brachial level, *Ephrin-B3* was expressed at the dorsal midline of the chick spinal cord. Dorsal midline axonal crossing was impeded following *Ephrin-B3* expression. Hence, supporting a role for gene-loss in shaping the circuitry at the wing level in avian spinal cord. To gain insight to the circuitry that enables refined bipedal locomotion, we searched for genetic access to interneurons that report the degree of lumbar motorneuron's activation to the cerebellum. Wiring analysis revealed that lumbar-level spinal interneurons dI2 integrate and report the degree of lumbar motorneuron's activation to cerebellum. The physiological role of dI2 neurons in chick locomotion was studied by inhibiting the neuronal activity of dI2. Kinematic analysis demonstrates uncoordinated bipedal gait following dI2-silencing in P8 hatchling chicks. We propose that in birds synchronous flapping of wings evolved through sequential inactivation of the *Ephrin-B3* gene, and the fidelity of bipedal locomotion is attained by dI2 neurons.

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ДНС SNS Друштво за неуронауке Србије Serbian Neuroscience Society
National Neuroscience Society of Romania
Neuroscience Society of Turkey

Saturday, July 13, 2019

11:30–13:10

Room Atlantic 2

Symposium 37

Behavioral, electrophysiological and tissue recovery after cerebral ischemia

Organizers: Aurel Popa Wagner (Craiova, RO) and Ana-Maria Zagrean (Bucharest, RO)

PHARMACOLOGICAL AND CELL-BASED THERAPIES OF CEREBRAL ISCHEMIA

Aurel Popa-Wagner

University of Medicine and Pharmacy Craiova, Craiova, Romania

aurel.popa-wagner@geriatrics-healthyageing.com

Attractive therapeutic strategies to enhance post-stroke recovery of aged brains include nutritional, drug, cell and genetic therapies that can enhance the odds of functional recovery and boost endogenous restorative mechanisms of the injured brain.

Nutrition: Obesity and hyperinsulinemia are risk factors for stroke. We tested the hypothesis that caloric restriction, which reduces the incidence of age-related obesity and metabolic syndrome, may represent an efficient and cost-effective strategy for preventing stroke and its devastating consequences. We showed that our study shows that recovery from stroke is enhanced in aged rats by a dietary regimen that reduces body weight prior to infarct.

Gaseous Hypothermia may have a pivotal role in post-ischemic recovery by (i) reducing the metabolic rate; (ii) stimulating angiogenesis; (iii) reducing the epileptic forms of EEG activity; and (iv) efficient in controlling and containing brain inflammation.

Chemoattractans and Cell therapies: We have shown that the chemoattractant G-CSF alone is effective in improving behavioral recovery after stroke in aged rats. In subsequent experiments we tested the hypothesis that treating post-stroke aged rats with the combination of bone marrow-derived mononuclear cells (BM MNC) or bone marrow-derived mesenchymal cells BM MSC and G-CSF might improve the long term (56 days) functional outcome. Also we also considered approaches involving the use of human iPS cells for treatment of post-stroke aged animal models featuring relevant co-morbidities.

Genetic conversion: restoring the balance between neurons and non-neuronal cells within the post-stroke perilesional area is crucial for post-stroke recovery. The latter idea has gained momentum following the discovery that in vivo direct lineage reprogramming in the adult mammalian brain is a feasible strategy for reprogramming non-neuronal cells into neurons; this exciting new technnology emerged as a new approach to circumvent cell transplantation.

Conclusion: To date, all monotherapeutic attempts to prevent or minimize brain damage after stroke have failed. In view of our findings that stroke disrupts the physiology, biochemistry, and gene expression of multiple central nervous systems in an age-dependent manner, the failure of therapies aimed at a single target system is perhaps inevitable.

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PROMOTING NEUROLOGICAL RECOVERY AND NEUROPLASTICITY IN THE ISCHEMIC BRAIN

Dirk M. Hermann

Chair of Vascular Neurology, Dementia and Ageing Research, Department of Neurology, University Hospital Essen, Germany

dirk.hermann@uk-essen.de

Following recent advances in acute stroke management, where mechanical recanalization therapies considerably reduced detrimental stroke consequences, there is a lack of treatments allowing us to reduce long-term consequences of ischemic stroke once ischemic injury has occurred. Presently major efforts are made to enhance stroke recovery by means of plasticity promoting therapies. In this presentation, therapeutic strategies on their way from the bench to bedside are reviewed and pitfalls endangering the success of clinical trials discussed.

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BEHAVIORAL, ELECTROPHYSIOLOGICAL AND TISSUE RECOVERY AFTER CEREBRAL ISCHEMIA

Organizers: Aurel Popa Wagner (Craiova, RO) and Ana-Maria Zagrean (Bucharest, RO)

PRENATAL MODULATION OF BRAIN VULNERABILITY TO ASPHYXIA IN RAT

Ana-Maria Zagrean[1], Anca Maria Panaitescu[1,2], Sebastian Isac[1], Alexandru Catalin Paslaru[1], Mara Ioana Iesanu[1], Alexandra Totan[1], Natalia Cucu[3], Mihai Moldovan[1,4], Leon Zagrean[1]

1Carol Davila University of Medicine and Pharmacy, Bucharest, Romania;
2Filantropia Clinical Hospital, Bucharest, Romania;
3Association for Epigenetics and Metabolomics, Bucharest; Romania;
4Neuroscience and Pharmacology, Panum, University of Copenhagen, Copenhagen, Denmark

ana-maria.zagrean@umfcd.ro

Asphyxia at birth is a leading cause of mortality and morbidity with long-term implications in the neonatal population. Dietary intake during pregnancy was shown to influence child neurodevelopment and cognitive function, and could impact its response to perinatal asphyxia (PA). This presentation will focus on the early and late effects of trans-resveratrol, citicoline and high-fat maternal dietary supplementation in offspring subjected to PA (90-minute exposure to 9% O_2 and 20% CO_2 in postnatal day 6 Wistar rat pups). The post-asphyxia seizure burden was evaluated by the cumulative loss of righting reflex during the first 2-hour post-exposure. The neuroinflammation (IL-1β and TNF-α) and injury (S100B protein) markers, as well as related epigenetic factors (non-coding microRNAs miR-15a, miR-34a, miR-124, miR-132, miR-134 and miR146) were assessed from hippocampal homogenate obtained 24 hours post-asphyxia. The late outcome was assessed at maturity by electrophysiology (electrocorticogram) and behavioral tests (open field test, novel object recognition test, T-Maze and forced swimming test). Our results indicate that maternal diet influences the immature brain vulnerability to asphyxia by epigenetic mechanisms, with possible early changes in the seizure burden, neuronal injury and inflammation, but also with late impact on electrophysiological and behavioral outcome. Trans-resveratrol and citicoline supplemented maternal diets have shown protective effects on offspring, while high-fat maternal diet triggered an early increase in neuronal injury and inflammation. Our data propose a novel perspective on the influence of maternal supplemented diet as potential epigenetic factor to modulate the offspring brain injury accompanying perinatal asphyxia.

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NEUROPHYSIOLOGICAL ASSESSMENT OF THE POST-ISCHEMIC BRAIN

Mihai Moldovan[1,2]

1Physiology and Fundamental Neuroscience, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; 2Department of Neuroscience, University of Copenhagen, Copenhagen, Denmark

moldovan@sund.ku.dk

The hypoxic ischemic brain injury (HIBI) is a leading cause of mortality and long-term neurologic disability in survivors. Characteristic to HIBI is that the primary brain insult is aggravated by secondary injuries during reperfusion and the subsequent period of microcirculatory dysfunction. Long-term monitoring of brain function recovery by electroencephalography (EEG) is required in addition to clinical scales for diagnosing the HIBI severity and prognostication. An increasing number of rodent models have been developed to assess neuroprotective strategies in HIBI, however, the differences between human and rodent EEG confounds the translation of neurophysiological biomarkers. Under deep anesthesia, the EEG of humans and rodents becomes discontinuous, comprising of busts of activity on a suppressed background. This raises the hypothesis that simplifying the electrical activity to a burst-suppression (BS) pattern, can provide a unique opportunity for translational EEG assessment. Somatosensory stimulation can reduce the suppression ratio (fraction of time spent in suppression) a process referred to as BS reactivity. Work I carried out with the international ComaEEG.RO consortium comprised of basic scientists, clinicians and industry partners, has led to the development of a translational BS reactivity index that can be used to assess HIBI. Our recent work suggests that continuous EEG can also be segmented to extract a binary class of somatosensory suppression referred to as the default EEG activity. We thus defined a generalized default EEG reactivity index (DERI, patent pending) that can be used to monitor BS and continuous EEG alike with extended applicability in stroke and other brain disorders.

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Symposium 38

Hypothalamic-pituitary system: physiological and cancer cell signaling pathway

Organizers: Stanko S. Stojilkovic (Bethesda, MD, USA)

HYPOTHALAMIC-VASCULAR-PITUITARY UNIT FUNCTION AND PLASTICITY

Lafont C[1], Fiordelisio T[2], Fontanaud P[1], Méry PF[1], Samper P[1], Deverdun J[1], Molino F[1], Guillou A[1], Boehm U[3], Rizzoti K[4], Lovell-Badge R[4], Mollard P[2].

1Physiology, Institute of Functional Genomics, Montpellier, France;
2Ecol. y Recursos Naturales, F. Ciencias, Universidad Nacional Autónoma de México, México City, México;
3Center for Molecular Neurobiology, Institute for Neural Signal Transduction, Hamburg, Germany, 4Francis Crick Institute, London, United Kingdom

tfiorde@ciencias.unam.mx

Signalling molecules undergo bidirectional transport across fenestrated capillaries. Molecules such as oxygen and metabolites are timely delivered to parenchymal cells in response to metabolic demands while secreted hormones and neurohormones need to reach the systemic circulation. However, there is only limited information about how these bidirectional transvascular processes are coordinated *in vivo*. Pericytes are traditionally described as mural cells which intimately interact with endothelial cells in microvessels. They are excitable cells and contain contractile proteins. Here, we unveil how pericytes directly control capillary blood flow and thereby exchanges at the level of the hypothalamus-pituitary portal system. In freely-behaving mice, pericytes display endogeneous calcium spikes. In *in vivo* anesthetized animals, the manipulation of pericyte activity triggers changes in both blood flow velocity, oxygen supply towards parenchymal cells, and transfer of macromolecules from the parenchyma towards capillary lumen. Varying pericyte-driven changes in blood flow result in predictable changes of circulating hormone levels. Our data suggest that pericytes are dynamically responsible for the bidirectional signal transmission across fenestrated capillaries, thus indicating the importance of targeting pericytes in hormonal and metabolic diseases.

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PURINERGIC SIGNALING IN HYPOTHALAMUS AND PITUITARY

Hana Zemková[1] and Stanko S. Stojilkovic[2]

1Department of Cellular and Molecular Neuroendocrinology, Institute of Physiology, Czech Academy of Sciences, Prague, Czech Republic; 2Section on Cellular Signaling, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, Bethesda, MD, USA

zemkova@biomed.cas.cz

ATP-gated P2X receptors (P2XRs) have numerous functions in neuronal and neuroendocrine cells, including the control of neurotransmitter and hormone release. P2XRs are well expressed throughout the hypothalamus, including the supraoptic and suprachiasmatic nuclei. The supraoptic neurons, the hypothalamic release site of vasopressin and oxytocin, express functional presynaptic and somatic P2X2R and P2X4R that control their electrical excitability and modulate glutamate and GABA release. The suprachiasmatic neurons, the circadian master clock in mammals, express presynaptic P2X2Rs that also modulate synaptic transmission. ATP is stored in secretory vesicles of suprachiasmatic astrocytes and rhythmically released in a Ca^{2+}-dependent and -independent manner, the later through P2X7R. Pituitary cells also express P2X2R, P2X4R, and P2X7R and release intracellularly stored ATP during agonist-induced exocytosis. The P2X4 subunit is the most abundant in pituitary gland, including lactotrophs, whereas the P2X2 subunit is expressed predominantly in folliculostellate cells and gonadotrophs. ATP-induced rapid depolarization of pituitary cells leads to initiation of firing in quiescent cells or increase in the frequency of action potentials in spontaneously active cells, coupled with a transient stimulation of hormone release. This indicates that P2XRs could operate as pacemaking channels and modulators of electrical activity and secretion in both hypothalamic and anterior pituitary cells.

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HYPOTHALAMIC-PITUITARY SYSTEM: PHYSIOLOGICAL AND CANCER CELL SIGNALING PATHWAY

Organizers: Stanko S. Stojilkovic (Bethesda, MD, USA)

A SINGLE - CELL TRANSCRIPTOME ATLAS OF THE ANTERIOR PITUITARY: 10X GENOMICS' NEW CHROMIUM SYSTEM

Patrick A. Fletcher[1], Kosara Smiljanic[2], Rafael Maso Previde[2], James Iben[3], Tianwei Li[3], Milos B. Rokic[2], Arthur Sherman[1], Steven L. Coon[3], and Stanko S. Stojilkovic[2]

1Laboratory of Biological Modeling, National Institute of Diabetes, Digestive and Kidney Diseases, NIH, Bethesda, MD, USA;
2Section on Cellular Signaling and 3Molecular Genomics Core, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, Bethesda, MD, USA

stankostojilkovic@gmail.com

Understanding of physiology and pathology of an organ composed of variety of cell populations is critically dependent on genome-wide information on each cell type. Here, we report single-cell transcriptome profiling of over 6800 freshly dispersed anterior pituitary cells from postpubertal male and female rats. A total of six pituitary-specific cell types were identified based on known marker genes and characterized: hormone producing corticotrophs, gonadotrophs, thyrotrophs, somatotrophs, and lactotrophs (but not bihormonal cells), as well as folliculostellate cells. Also identified were endothelial and blood cells from the pituitary capillary network. The expression of numerous developmental and neuroendocrine marker genes in both folliculostellate and hormone producing cells supports that they have a common origin. For several genes, the validity of transcriptome analysis was confirmed by single cell immunochemistry and qRT-PCR. Folliculostellate cells exhibit impressive transcriptome diversity, indicating their major roles in production of endogenous ligands and detoxification enzymes, and organization of extracellular matrix. Transcriptome profiles of hormone producing cells also indicate contributions toward those functions, while clearly demonstrating their endocrine function. This survey also highlights many novel genetic markers contributing to pituitary cell type identity, sexual dimorphism, and function and points to relationships between hormone producing, folliculostellate, and endothelial cells.

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FROM PITUITARY ADENOMA TO AGGRESSIVE PITUITARY TUMOR: NOT NEAR YET!

Vera Popovic

Faculty of Medicine, University Belgrade, Belgrade, Serbia

popver@gmail.com

Pituitary adenomas grow slowly, enlarge by expansion, become demarcated from normal pituitary and usually do not produce any symptoms. They arise from any of the five differentiated cell types within the gland (GH, PRL, TSH, ACTH, FSH/LH). Pituitary adenomas are benign and associated with specific endocrine syndromes.When less than 1 cm in size they are microadenomas, which appear to stop growing. What limits their ability to proliferate is still unknown. Vast majority of pituitary adenomas are trophically stable and change little in size over many years. What did we learn from hereditary pituitary tumors? Hereditary (familial)syndromes associated with pituitary tumors are: MEN-I, the hereditary endocrine-cancer syndrome with more than 1000 germline mutations in the MEN-I gene (tumor suppressor gene), McCune-Albright syndrome, resulting from activating mutations of the cAMP regulatory protein (GNAS1 gene product Gsα-oncogene), Carney Complex, the genetic multiple neoplasia syndrome skin-cardiac-endocrine tumors (mutations in the regulatory subunit 1A of the protein kinase A-PRKAA1-tumor suppressor gene). FIPA are familial pituitary tumors (at least two members in family have pituitary tumors) that have loss of function mutations in the gene encoding Aryl Hydrocarbon receptor Interacting Protein (AIP-tumor suppressor gene). Clinical implication of hereditary pituitary tumors is that they are more aggressive, occur in young and allow prospective screening of patients at young age. A comparatively small proportion of sporadic pituitary tumors behave more aggressively and come to clinical attention through inappropriate hormone secretion or adverse effects on surrounding structures (invasion). Genetic and epigenetic studies in these sporadic but aggressive pituitary tumors did not yield any positive results i.e. we are not yet there! A new clinico-pathological five-tiered classification of pituitary neuroendocrine tumors (pitNETs) considers invasion, the immunohistological subtype, and proliferation markers (Ki-67 index, mitotic count, p53 positivity) which may allow earlier diagnosis of aggressive pituitary tumors in whom there is a need to commence aggressive treatment prior to the occurrence of metastases.

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Symposium 39

Molecules for mind: how remote is the link?

Organizers: Pavel Balaban (Moscow, RU) and Konstantin Anokhin (Moscow, RU)

CLEAVING PROTEINS AT THE SYNAPSE TO LINK BRAIN AND MIND

Leszek Kaczmarek

Nencki Institute, Warsaw, Poland

l.kaczmarek@nencki.gov.pl

Matrix metalloproteinase 9, MMP-9 is an extracellularly operating enzyme that has been demonstrated as important regulatory molecule in control of synaptic plasticity, learning and memory. We have shown that either genetic or pharmacological inhibition of MMP-9 impairs synaptic plasticity in the brain, as well as certain forms of learning and memory formation. MMP-9 is locally translated and released from the excitatory synapses in response to neuronal activity. Extrasynaptic MMP-9 is required for growth and maturation of the dendritic spines to accumulate and immobilize AMPA receptors, making the excitatory synapses more efficacious. Our studies on animal models have implicated MMP-9 in such neuropsychiatric conditions, as e.g., epileptogenesis, autism spectrum disorders, development of addiction, and depression. We have also reported that in humans MMP-9 appears to contribute to epilepsy, alcohol addiction, Fragile X Syndrome, schizophrenia and bipolar disorder. In aggregate, all those conditions may be considered as relying on alterations of dendritic spines/excitatory synapses and thus understanding the role played by MMP-9 in the synaptic plasticity may allow to elucidate the underpinnings of major neuropsychiatric disorders.

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SYMPOSIUM 39

MOLECULES FOR MIND: HOW REMOTE IS THE LINK?

Organizers: Pavel Balaban (Moscow, RU) and Konstantin Anokhin (Moscow, RU)

MOLECULAR WAYS OF MEMORY MAINTENANCE REGULATION

Pavel Balaban

Inst. Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Moscow, Russia

pmbalaban@gmail.com

Recently it was shown that the reinforcing neurotransmitter serotonin is necessary for successful repeated reconsolidation of context memory in terrestrial snails. We used injection of the serotonin precursor 5-HTP for reinstatement of memory after its impairment during reconsolidation with a protein synthesis blocker or with a specific inhibitor (ZIP) of atypical proteinkinase PkMzeta shown to be involved in memory maintenance. It was found that application of 5-HTP known to increase the serotonin concentration or just reminding did not restore the context memory, while combination of 5-HTP+reminder effectively reinstated the impaired context memory. Application of an epigenetic regulator, histone deacetylase inhibitor sodium butyrate (NaB), was not as effective as serotonin, and the reminder+NaB reinstated memory only partially after impairment with ZIP, while additional session of training under NaB effectively reinstated the impaired memory. Application of an inhibitor of DNA methyltransferases RG108 impaired the context memory, and the memory was not reinstated by reminder or additional training session, while NaB+reminder and NaB+training partially reinstated the memory. Obtained data confirmed the assumption that the reinforcing transmitter (serotonin) is necessary for successful reconsolidation, demonstrated possible ways of memory regulation during the reconsolidation process by the epigenetic factors.

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GENETIC TRAPPING AND IMAGING OF ENGRAMS CELLS

Konstantin Anokhin

Department of Neuroscience, National Research Center "Kurchatov Institute", Moscow, Russia;
Institute for Advanced Brain Studies, Lomonosov Moscow State University, Moscow, Russia;
P.K.Anokhin Research Institute of Normal Physiology, Moscow, Russia

k.anokhin@gmail.com

Our approach to study engrams exploits the experience-dependent expression of immediate early genes (IEGs). Consolidation of memory involves expression of IEGs and they can be used to map engrams in the brain. Currently we label engram neurons by targeted recombination in active populations (TRAP) strategy which exploits experience-dependent Cre-loxP recombination in neurons of Fos-CreERT2 and Arc-CreERT2 mice crossed to various Cre-reporter lines. Trapped engram neurons can be then co-labelled by classical IEGs immunohistochemistry during memory retrieval, extinction or association with other experiences. Combined with techniques of optical clearing and whole brain microscopy these approaches enable large-scale imaging of cellular allocation, co-allocation and dynamics of engrams. We also employ a variation of TRAP strategy based on double immunostaining for endogenous c-Fos and Cre-recombinase expressed under the *c-fos* promotor. In such experiments immunostaining for c-Fos and Cre is performed at different time points after the training. This strategy allows to compare neurons that were activated in two cognitive episodes spaced by 3-8 h. In addition we use Fos-Cre-GCaMP transgenic mice to image long-term calcium activity in cognitively indexed neurons. For this purpose, we introduce GCaMP3 sensor into TRAPed neurons of mice that were exposed to an episode of a new experience. The total number of GCaMP3 positive neurons reaches maximum 72 h after that and remains stable for at least two months allowing to study populations of cognitively indexed neurons trapped during specific episodes of subjective experience.

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SYMPOSIUM 40

THE AGING BRAIN: MECHANISMS AND INTERVENTIONS

Organizers: Dan Ehninger (Bonn, DE) and Selma Kanazir (Belgrade, RS)

LIFESPAN AND HEALTHSPAN IN MICE: MECHANISMS AND INTERVENTIONS

Dan Ehninger

German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

Dan.Ehninger@dzne.de

Aging is a major risk factor for a range of adult-onset disorders, including neurodegenerative diseases, and is associated with a broad range of functional impairments. Targeting aging processes with suitable pharmacological, dietary or behavioral interventions could potentially represent a powerful inroad for the development of preventatives or treatments for aging-associated disorders. A large number of genes and pathways have been identified that extend lifespan in invertebrates as well as in mice but more needs to be learned about possible healthspan effects that corresponding interventions may have. In this presentation, I will share data on how aging phenotypes unfold across the lifespan in mice. I will also discuss the question to what extent lifespan-extending manipulations slow mammalian aging rates and promote overall healthy aging in mammals on the level of organs and tissues, including the brain.

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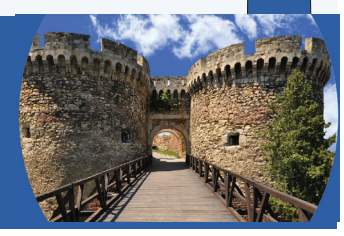

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Organizers: Dan Ehninger (Bonn, DE) and Selma Kanazir (Belgrade, RS)

PROTEASOME ACTIVATION DELAYS AGING AND PROGRESSION OF AGE-RELATED DISEASES

Efstathios S. Gonos[1], Selma Kanazir[2], Aleksandra Mladenovic Djordjevic[2]

1National Hellenic Research Foundation, Institute of Biology, Medicinal Chemistry & Biotechnology, Athens, Greece;
2Institute for Biological Research "Sinisa Stankovic", University of Belgrade, Belgrade, Serbia

sgonos@eie.gr

Aging and longevity are two multifactorial biological phenomena whose knowledge at molecular level is still limited. We have studied proteasome function in replicative senescence and cell survival (Mol Aspects Med 35, 1-71; Ageing Res Rev 23, 37-55). We have observed reduced levels of proteasome content and activities in senescent cells due to the down-regulation of the catalytic subunits of the 20S complex (J Biol Chem 278, 28026-28037). In support, partial inhibition of proteasomes in young cells by specific inhibitors induces premature senescence which is p53 dependent (Aging Cell 7, 717-732). Stable over-expression of catalytic subunits or POMP resulted in enhanced proteasome assembly and activities and increased cell survival following treatments with various oxidants. Importantly, the developed "proteasome activated" human fibroblasts cell lines exhibit a delay of senescence by approximately 20% (J Biol Chem 280, 11840-11850; J Biol Chem 284, 30076-30086). Similar proteasome activation in human mesenchymal stem cells not only increases their lifespan, but also enhances stemness significantly (Free Rad Biol Med 103, 226-235). Moreover, additional findings indicate that the recorded proteasome activation by many inducers is Nrf2-dependent (J Biol Chem 285, 8171-8184). In a complimentary work, we provide evidence that proteasome activation is an evolutionary conserved mechanism, as it can delay aging in vivo and, importantly, it also confers deceleration of aggregation-related pathologies, such as Alzheimer's (AD) or Huntington's diseases (FASEB J 29, 611-622). Given these findings, recent work has identified a proteasome activator that decelerates aging and Alzheimer's disease progression and pathology in lower eukaryotes (Antiox Redox Signal 25, 855-869) as well as a mouse model (unpublished data).

There are no financial interests to disclose

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THE AGING BRAIN: MECHANISMS AND INTERVENTIONS

Organizers: Dan Ehninger (Bonn, DE) and Selma Kanazir (Belgrade, RS)

EFFECTS OF WORKING MEMORY TRAINING IN ADULT AND AGED MICE ON COGNITIVE FUNCTION

Kyriaki Sidiropoulou

University of Crete and Institute of Molecular Biology and Biotechnology – Foundation for Research and Technology Hellas, Greece

sidirop@imbb.forth.gr

Working memory (WM) is a type of short-term memory that allows for on-line maintenance and manipulation of information. WM is also involved in cognitive flexibility and long-term memory. WM training could be beneficial as it could enhance WM capacity and different cognitive functions. However, we still do not understand the neurobiological basis that could explain the beneficial effects of WM training. In my lab, we investigate the effects of WM training in adult and aged mice, by subjecting them to the delayed alternation task for 9 days. Following the end of WM training, we examine both other cognitive functions and anatomical and physiological measurements in the prefrontal cortex and the hippocampus. We have found that trained adult mice improve their performance in the attention set-shifting task and reversal learning, but not in the left-right discrimination task, compared to untrained mice. Trained adult mice also exhibit changes in the dimensions of the prefrontal cortex and the hippocampus, as measured from Nissl-stained brain slices, enhanced long-term potentiation in their prefrontal cortex and increased synaptic transmission in the hippocampus, and changes in dendritic spine density. However, male, aged (20-month-old) trained mice do not show improvements in reversal learning or performance in the left-right discrimination task, compared to untrained mice. Furthermore, no changes were found in dendritic spine density. Our results indicate that WM training affects, in an age-dependent manner, performance in specific behavioral tasks, in particular those requiring cognitive flexibility, and underlying neuroanatomical and neurophysiological properties.

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DIETARY RESTRICTION AS THE NEUROPROTECTIVE STRATEGY: THE IMPACT OF ONSET AND DURATION

Smilja Todorovic, Milica Prvulovic, Kosara Smiljanic, Selma Kanazir, Aleksandra Mladenovic Djordjevic

Institute for Biological Research "Sinisa Stankovic", University of Belgrade, Belgrade, Serbia

anamikos@ibiss.bg.ac.rs

Dietary restriction (DR) is widely considered as universally beneficial environmental manipulation. It increases the life span, delays aging and age-related disease. However, the impact of dietary restriction could depend of the type of restriction, its onset and duration. The aim of this study was to investigate the effects of different dietary paradigms, starting from a very restrictive diet, to the intermittent fasting. Male Wistar rats were used and DR was introduced at different time points during life, including adults (6-month-old), middle aged (12-, 15- or 18-month-old) and old (18 and 21 months) animals. DR-induced effects at both behavioral and molecular level were investigated. Frailty status of the animal, motor and cognitive abilities and anxiety level were determined. By using PCR and Western blot techniques we revealed age- and DR-related changes in synaptic plasticity, dopaminergic pathways, and cholesterol metabolism in the relevant brain structures. We found that the effect of DR significantly depends of the onset and duration of a diet, varying from undoubtedly beneficial to harmful one.

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Room Atlantic 1

SYMPOSIUM 41

DISSECTING NEURAL CIRCUITS OF BEHAVIOR

Organizers: Gulsen Surmeli (Edinburgh, UK) and Asli Ayaz (Zurich, CH)

SENSORIMOTOR INTEGRATION IN PRIMARY SENSORY CORTICES

Andreas Stäuble, Fritjof Helmchen, Aslı Ayaz

University of Zurich, Brain Research Institute, Zurich, Switzerland

ayaz@hifo.uzh.ch

We perceive the outside world as a result of sensorimotor interactions and processing of even simple stimuli varies greatly at different behavioral states. Effects of active behavior, i.e. locomotion, on visual processing have been widely explored. However findings cannot be generalized to other sensory modalities as modulations vary. Particularly vibrissae somatosensory processing during locomotion presents a more complicated paradigm as running is almost always accompanied by whisking, which is by itself considered an active state. In this study we investigate how locomotion modulates neuronal activity in somatosensory cortex and how it is integrated with whisker touch. We used two-photon calcium imaging of several classes of neurons in head-restrained mice running in a novel tactile virtual reality setup. About a third of excitatory neurons increased their activity during running and concomitant whisking, in the absence of touch. Fewer neurons were modulated by whisking alone (<10%). Layer specific responses arose during sensory stimulation: L5 neurons responded transiently to touch during running whereas L2/3 neurons showed sustained activity. Consistently, neurons encoding running-with-touch were more abundant in L2/3 compared to L5 suggesting more integrative roles for superficial neurons. To explore the role of inhibitory neurons during locomotion-dependent sensory processing we measured neural activity in transgenic mice expressing calcium indicator in different inhibitory cell classes: vasoactive intestinal peptide (VIP+), somatostatin (SOM+) or parvalbumin-positive (PV+) interneurons. VIP+ neurons uniformly showed increased response during active states, whereas PV+ and SOM+ neurons showed diverse response patterns. Functional clustering of SOM+ and PV+ responses revealed multiple subtypes with distinct modulations during state-dependent tactile processing.

Supported by: European Research Council (ERC Advanced Grant BRAINCOMPATH, project 670757; F.H.), SNSF Marie Heim-Vögtlin grant (PMPDP3_145476; A.A.) and SNSF Ambizione grant (PZ00P3_161544; A.A.).

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SYMPOSIUM 41

DISSECTING NEURAL CIRCUITS OF BEHAVIOR

Organizers: Gulsen Surmeli (Edinburgh, UK) and Asli Ayaz (Zurich, CH)

PATHWAYS FOR BRIDGING THE MEMORY HUBS OF THE BRAIN

Sau Yee Tsoi, Merve Öncül, Zuzanna Bogdanowicz, Gülşen Sürmeli

University of Edinburgh, Edinburgh, United Kingdom

gsurmeli@ed.ac.uk

Long-term memory involves interactions dispersed across cortical circuits, but how these interactions are coordinated is not known. Because of its input from the hippocampus and wide ranging projections to cortical systems, the entorhinal cortex (EC) might play a pivotal role in the formation and coordination of cortical memory networks. However, organising principles for distribution of entorhinal projections to the cortex have not been established and how these projections play roles in the formation and shaping of cortical network activity is unknown. We investigated the range of targets of entorhinal projection neurons using whole brain imaging of fluorescently labelled axons. We confirmed and extended previous findings and revealed that the EC has a very wide target range. We then carried out high-throughput single cell projection mapping to delineate the projection motives of entorhinal projection neurons. Our data suggests that EC output has distinct patterns. Instead of broadcasting the same message to all targets single neurons have a select set of projection targets.

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SYMPOSIUM 41

DISSECTING NEURAL CIRCUITS OF BEHAVIOR

Organizers: Gulsen Surmeli (Edinburgh, UK) and Asli Ayaz (Zurich, CH)

MODULATION OF HYPOTHALAMIC HUNGER CIRCUITS BY AN ASCENDING CATECHOLAMINE PATHWAY

Atasoy Deniz

University of Iowa, Iowa City, USA

deniz-atasoy@uiowa.edu

Hunger is a hard-wired behavioral state essential for survival. Hunger sensitive agouti-related protein (AgRP)-expressing neurons of arcuate hypothalamic nucleus (ARC) play central role in feeding, yet the signals that modulate AgRP neuron activity are poorly understood. We discovered that tyrosine hydroxylase (TH)-expressing neurons from nucleus of solitary tract (NTS) project densely to the hypothalamus, and their local activation elicit voracious feeding through bidirectional regulation of AgRP and proopiomelanocortin (POMC)-expressing neurons. Neuroanatomical tracing results suggested that ARC projecting orexigenic NTS^{TH} neurons comprise a largely distinct subpopulation than those parabrachial nucleus (PBN)-projecting anorexigenic NTS^{TH} neurons. Finally, optogenetic and chemogenetic analyses showed that norepinephrine (NE)-signaling from NTS^{TH} terminals in the ARC is critical for appetite stimulation. Collectively, we describe a circuit organization in which an ascending neuromodulatory pathway from brainstem coordinates key appetite neurons in hypothalamus for rapid regulation of hunger.

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DISSECTING NEURAL CIRCUITS OF BEHAVIOR

Organizers: Gulsen Surmeli (Edinburgh, UK) and Asli Ayaz (Zurich, CH)

NEURONAL ENSEMBLES UNDERLYING INTERNALLY-GENERATED REPRESENTATIONS

George Dragoi

Departments of Psychiatry and Neuroscience, Yale School of Medicine, New Haven, CT, USA

george.dragoi@yale.edu

A central goal in learning and memory research is to reveal the neural substrates underlying episodic memory formation. The hallmark of sequential spatial trajectory learning, a model of episodic memory, has remained equivocal, with proposals ranging from de novo creation of compressed sequential reactivations/replay from blank-slate networks to selection of pre-existing compressed preplay sequences. In my talk, I will show that increased millisecond-timescale activation of cell-assemblies expressed during de-novo sequential experience and increased neuronal firing-rate correlations can explain the difference between post-experience trajectory replay and robust preplay. In contrast, changes in overall neuronal/cell-assembly temporal order within extended sequences do not account for sequential trajectory learning. We propose the coordinated strengthening of cell-assemblies played sequentially on robust pre-existing temporal frameworks could support rapid formation of episodic-like memory.

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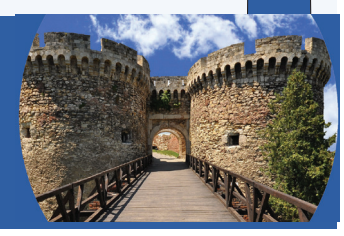

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Symposium 42

Understanding the role of GPCR heteroreceptor complexes in the neuronal networks of the brain in health and disease

Organizers: Dasiel O. Borroto-Escuela (Stockholm, SE) and Gemma Navarro (Barcelona, ES)

SIGNALING AT D2R-OXYTOCIN HETEROCOMPLEXES AND THEIR RELEVANCE FOR THE AXIOLYTIC EFFECTS OF D2R-OXYTOCINR INTERACTIONS IN THE AMYGDALA OF THE RAT

M Pérez de la Mora[1], D Pérez-Carrera[1], AD Hernández-Hernández[1], M Crespo-Ramírez[1], K Fuxe[2], DO Borroto-Escuela[2]

1Instituto Fisiologia Celular, Universidad Nacional Autónoma de México, Mexico City, Mexico;
2Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden

mperez@ifc.unam.mx

Aims: Our aim was to ascertain whether amygdaloid dopamineD2R-oxitocinR interactions with relevance for anxiety do exist and to study their possible signaling mechanisms.

Methods: Drugs were stereotaxically infused into the amygdala. Behaviour was evaluated in the Shock-Probe Burying test. Signaling experiments were carried out in co-transfected HEK293 cells through CREB, SRE, NFkB and NFAT gene reporter analysis.

Results: Behaviorally, dopamine D2R-oxitocinR interactions were disclosed since anxiolytic effects were observed following co-infusion of subthreshold doses of oxytocin and quinpirole, a D2 receptor agonist. Additionally, D2 receptor blockade suppressed the anxiolytic effects of oxytocin. CREB reporter gene assay indicated that oxytocin markedly enhanced the potency of quinpirole to inhibit the forskolin induced increase of the CREB signal. Furthermore, the oxytocin was found to increase the quinpirole potency to activate the MAPK pathway as studied with luciferase reporter gene assay measuring the degree of SRE activity. It was also observed that quinpirole markedly increased the oxytocin potency to activate the MAPK pathway. The extent of oxytocin-induced activation of PLC by Gq/11 coupled G protein (NFkB/NFAT) was studied using the NFkB- and NFAT-luciferase reporter assay and was observed that quinpirole shifts the OXTR agonist concentration-response of NFAT activity significantly to the left only in D_{2L}R-NTS1R co-transfected cells.

Conclusions: Our results support the presence of amygdaloid D2R-Oxytocin interactions with relevance for anxiety and show that they may involve synergistic allosteric receptor-receptor interactions in D_2R- OXTR heteroreceptor complexes.

Work supported by grant IN205217 from Dirección General de Asuntods del Personal Académico, Uninversidad Nacional Autónoma de México.

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SYMPOSIUM 42

UNDERSTANDING THE ROLE OF GPCR HETERORECEPTOR COMPLEXES IN THE NEURONAL NETWORKS OF THE BRAIN IN HEALTH AND DISEASE

Organizers: Dasiel O. Borroto-Escuela (Stockholm, SE) and Gemma Navarro (Barcelona, ES)

THE GPCR-HETNET: A NETWORK OF INTERACTING AND NON-INTERACTING G PROTEIN-COUPLED RECEPTOR PROTOMERS

Michael Di Palma[1], Ismel Brito[2], Manuel Narvaez[3], Stefano Sartini[1], Kamila Skieterska[4], Kathleen Van Craenenbroeck[4], Ismael Valladolid-Acebes[5], Malgorzata Filip[6], Riccardo Cuppini[1], Alicia Rivera[7], Fang Liu[8], Patrizia Ambrogini[1], Miguel Pérez de la Mora[9], Kjell Fuxe[2], and Dasiel O. Borroto-Escuela[2]

1Department of Biomolecular Sciences, University of Urbino Carlo Bo, Urbino, Italy;
2Department of Neuroscience, Karolinska Institute, Stockholm, Sweden;
3Instituto de Investigación Biomédica de Málaga, Facultad de Medicina, Universidad de Málaga, Málaga, Spain;
4Laboratory of GPCR Expression and Signal Transduction (L-GEST), Ghent University, Ghent, Belgium;
5The Rolf Luft Research Center for Diabetes and Endocrinology, Karolinska Institutet, Karolinska University Hospital L1, Stockholm, Sweden;
6Institute of Pharmacology, Polish Academy of Sciences, Department of Drug Addiction Pharmacology, Smetna, Kraków, Poland;
7Universidad de Málaga, Instituto de Investigación Biomédica, Facultad de Ciencias, Málaga, Spain;
8Campbell Research Institute, Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada;
9Instituto de Fisiología Celular, Universidad Nacional Autónoma de México, Circuito Exterior s/n, Ciudad Universitaria, Mexico City, Mexico.

michael.dipalma@uniurb.it

The G protein-coupled receptor heterocomplex network database (GPCR-hetnet) is a freeware web-database designed to store information on GPCR heteroreceptor complexes and their allosteric receptor-receptor interactions in humans. It is an expert-authored and peer-reviewed, curated collection of well documented GPCR–GPCR interactions that span the gamut from classical GPCR–GPCR interactions to more complex receptor-receptor interactions (GPCR-Receptor Tyrosine Kinase and GPCR ionotropic receptor/ligand-gated ion channel). Currently, GPCR-hetnet contains information on more than 250 receptors and more than 1023 interactions. The GPCR hetnet provides four searchable datasets: the hetnet, the non-hetnet (noninteracting protomers), the rtknet (GPCR–RTK interaction network database), and the ionnet (GPCR-ionotropic receptor interaction network database). Other supporting datasets include information about receptors that are present in GPCR-hetnet such as literature citations. This plethora of features makes the GPCR-hetnet a time-saving interactive toolbox to navigate the complexity of GPCR heteroreceptor complexes.

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Organizers: Dasiel O. Borroto-Escuela (Stockholm, SE) and Gemma Navarro (Barcelona, ES)

BRAIN 5-HT1A HETERORECEPTOR COMPLEXES IN A RAT MODEL OF DEPRESSION AND AS A TARGETS FOR ANTIDEPRESSANT TREATMENT.

Dasiel O. Borroto-Escuela[1, 2, 3], Caitlin M. DuPont[1], Xiang Li[1], David Savelli[1, 2], Davide Lattanzi[2], Ipsit Srivastava[1], Manuel Narváez[4], Michael Di Palma[2], Yuniesky Andrade-Talavera[5], Riccardo Cuppini[2], Yuji Odagaki[6], Miklos Palkovits[7], Patrizia Ambrogini[2], Maria Lindskog[1], Kjell Fuxe[1,*]

1Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden;
2Department of Biomolecular Sciences, University of Urbino Carlo Bo, Urbino, Italy;
3Observatorio Cubano de Neurociencias, Grupo Bohío-Estudio, Yaguajay, Cuba;
4Universidad de Málaga, Instituto de Investigación Biomédica de Málaga, Facultad de Medicina, Málaga, España;
5Center for Alzheimer Research, Neuronal Oscillations Lab, Karolinska Institutet, Stockholm, Sweden;
6Department of Psychiatry, Faculty of Medicine, Saitama Medical University, Saitama, Japan;
7Semmelweis University, Budapest, Hungary.

dasiel.borroto.escuela@ki.se

In recent studies [1,2] evidence is given for the existence of FGFR1-5-HT1A heterocomplexes based on the use of the *in situ* PLA [3]. They are involved in neuroplasticity in the rat hippocampus. Based on these findings [2]Dasiel O.</author><author>Romero-Fernandez, Wilber</author><author>Mudó, Giuseppa</author><author>Pérez-Alea, Mileidys</author><author>Ciruela, Francisco</author><author>Tarakanov, Alexander O.</author><author>Narvaez, Manuel</author><author>Di Liberto, Valentina</author><author>Agnati, Luigi F.</author><author>Belluardo, Natale</author><author>Fuxe, Kjell</author></authors></contributors><titles><title>Fibroblast growth factor receptor 1– 5-hydroxytryptamine 1A heteroreceptor complexes and their enhancement of hippocampal plasticity</title><secondary-title>Biol. Psychiatry</secondary-title></titles><periodical><full-title>Biol. Psychiatry</full-title></periodical><pages>84-91</pages><volume>71</volume><number>1</number><keywords><keyword>Allosteric modulation</keyword><keyword>depression</keyword><keyword>fibroblastgrowthfactorreceptor</keyword><keyword>heteroreceptor</keyword><keyword>neuronal plasticity</keyword><keyword>serotonin receptors</keyword></keywords><dates><year>2012</year></dates><isbn>0006-3223</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/pii/S0006322311009097</url></related-urls></urls><electronic-resource-num>10.1016/j.biopsych.2011.09.012</electronic-resource-num></record></Cite></EndNote> the hypothesis was tested if disturbances in the combined receptor agonist regulation of FGFR1-5-HT1A heterocomplexes can take place in a selectively bred rat model of depression, the Flinders sensitive line rat (FSL), using the naive SD rat as a control [4]. In control SD rats, the FGFR1 agonist SUN11602 and FGF2 produced a significant reduction of GIRK currents induced by 8-OH-DPAT in the CA1 area of the hippocampus. In FSL rats, only i.c.v. 8-OH-DPAT alone treatment produced a significant reduction in the immobility time. The combined i.c.v. treatment (FGF2 + 8-OH-DPAT) in FSL rats did not cause a significant decrease in immobility time in the forced swim test. However, in the SD rats this combined treatment produced a significant reduction. Furthermore, in the FSL rat a significant increase in the density of FGFR1-5-HT1A PLA positive clusters was only found after i.c.v. 8-OH-DPAT treatment alone in the CA2 and CA3 areas. In the SD rat a significant increase in the density of specific PLA clusters was only observed in the CA2 area of the i.c.v. combined treatment group. The results indicate that in FSL rats compared with SD rats alterations may develop in the ability of 8-OH-DPAT and combined FGFR1 and 5-HT1A agonist treatment to increase the density of FGFR1-5-HT1A heterocomplexes.

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Understanding the role of GPCR heteroreceptor complexes in the neuronal networks of the brain in health and disease

Organizers: Dasiel O. Borroto-Escuela (Stockholm, SE) and Gemma Navarro (Barcelona, ES)

PURINERGIC SIGNALLING IN PARKINSON'S DISEASES. RELEVANCE FOR TREATMENT

Gemma Navarro Brugal[1,2], Dasiel Borroto-Escuela[3], Jasmina Jimenez Cano[2,4], Kjell Fuxe[3] and Rafael Franco[2,4]

1Department of Biochemistry and Fisiology, University of Barcelona, Barcelona, Spain; 2CIBERNED. Centro de investigación en red en enfermedades neurodegenerativas. Instituto de Salud Carlos III. Madrid. Spain. 3Department of Neurosciences.Karolinska Institututed. Stockholm, Swden. 4Department of Biochemistry and Molecular Biology, University of Barcelona, Barcelona, Spain

g.navarro@ub.edu

Modulation of the levels of the endocannabinoid 2-arachidonoyl-glycerol by inhibiting monoacylglycerol lipase alters glial phenotypes and provides neuroprotection in a mouse model of Parkinson's disease. The fatty acid amide hydrolase inhibitor, URB597, administered chronically to mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and probenecid (MPTPp) over 5weeks prevented MPTPp induced motor impairment but it did not preserve the dopamine levels in the nigrostriatal pathway. The symptomatic relief of URB597 was confirmed in haloperidol-induced catalepsy assays, where its anti-cataleptic effects were both blocked by antagonists of the two cannabinoid receptors (CB_1 and CB_2), and abolished in animals deficient in these receptors. These results demonstrated an effect of fatty acid amide hydrolase inhibition on the motor symptoms of Parkinson's disease in two distinct experimental models that is mediated by cannabinoid receptors in both neurons and glia (Celorrio et al., 2016). The hypothesis of direct interactions between pairs of G-protein-coupled receptors relevant for CNS function, launched by Luigi Agnati and Kjell Fuxe, has been confirmed and is now widely accepted. Natural and synthetic cannabinoids target two types of G-protein-coupled receptors (GPCRs). Cannabinoid CB_1 receptors, which are enriched in the CNS and cannabinoid CB_2 receptors that are more abundant in peripheral tissues. Despite the moderate expression of CB_2 receptors in brain, it has been demonstrated that CB_1 and CB_2 may for receptor heteromers (RHets) in the CNS. Therefore, natural or synthetic cannabinoids may act on CB_1, CB_2 and CB_1 or CB_2 containing heteromers. The research presented in this paper was undertaken to know whether these two receptors may be expressed in activated microglia. It is worth noting that current knowledge assumed that CB_1 is more a neuronal than glial receptor whereas the opposite occurs for CB_2. On the one hand, the expression of receptors and RHets is different in resting and activated microglia. Activation was assayed in the N9 cell line and in primary cultures of microglia using LPS and interferon gamma. On the other hand, the increase in CB_1-CB_2 RHets correlates with a potentiation of the effects of selective CB_2 receptors. Our results show that the composition of cannabinoid receptors and RHets in resting microglia prevent microglia activation while in conditions of microgliosis due to Parkinsonian conditions, cannabinoid agonist regulate microglial activation. The results indicate that pharmacological manipulation of cannabinoid receptors in conditions of neuroinflammation may have relevant benefits in conditions of neuroinflammation.

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SYMPOSIUM 43

REGIONAL MINI SYMPOSIUM

Moderators: Emel Ulupinar (Istanbul, TR), Aleksandra Isakovic (Belgrade, RS), Ana-Maria Zagrean (Bucharest, RO)

SLEEP ALTERATIONS IN EPILEPSY AND ALZHEIMER'S DISEASE: FOCUS ON SHARED MECHANISMS

Dragan Hrnčić, Željko Grubač, Nikola Šutulović, Marko Vorkapić, Anida Ademović, Aleksandra Rašić-Marković, Olivera Stanojlović

Laboratory of Neurophysiology, Institute of Medical Physiology "Richard Burian", Belgrade University Faculty of Medicine, Belgrade, Serbia

drhrncic@yahoo.com

Translational and clinical studies suggested certain lifestyle factors may be important modulators of epilepsy and Alzheimer's disease, elucidating those related to sleep as particularly important. A significant breakthrough has been made in sleep medicine and it is quite clear that sleep is active, precisely regulated and vital physiological process. Shift work, some diseases and biorhythm changes caused by modern lifestyles are accompanied by quantitative and qualitative changes in sleep and the architecture of sleep. However, bidirectional relationship between sleep and epilepsy, and sleep and Alzheimer's disease have not yet been fully understood, despite the high prevalence of these neurological disorders and their overall importance. Paradoxical sleep deprivation potentiated development of epileptic activity, as demonstrated in several experimental models of epilepsy. According to our results, these effects persist despite the fact that this manipulation leads to a decrease in homocysteine, which is excitatory neuromodulator and risk factor for Alzheimer's disease. Moreover, poor sleep quality is significant modulator of epileptic activity and is shown to be potential marker of Alzheimer's disease. Sleep fragmentation accompanying sleep apnea and related disorders potentiated facilitated induction of seizures, as shown by our behavioral and electroencephalographic study. We showed that sleep fragmentation induces variety of alterations in hormonal and cytokines profile in different brain structures being recognized as important mechanisms for development of both epilepsy and Alzheimer's disease. Other mechanisms will be also discussed. Good quality of sleep is beneficial for epilepsy patients, while it may prevent delay and onset of Alzheimer's disease in people at risk.

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REGIONAL MINI SYMPOSIUM

Moderators: Emel Ulupinar (Istanbul, TR), Aleksandra Isakovic (Belgrade, RS), Ana-Maria Zagrean (Bucharest, RO)

INHIBITION OF AQUAPORIN-4 IMPROVES THE OUTCOME OF ISCHAEMIC STROKE AND MODULATES BRAIN PARAVASCULAR DRAINAGE PATHWAYS

Pirici I[1], Catalin B[2], Balsanu TA[2], Margaritescu C[3], Mogoanta L[4], Pirici D[5], Carare RO[6], Muresanu DF[7]

1Department of Human Anatomy, University of Medicine and Pharmacy of Craiova, Craiova, Romania;
2Department of Physiology, University of Medicine and Pharmacy of Craiova, Craiova, Romania;
3Department of Pathology, University of Medicine and Pharmacy of Craiova, Craiova, Romania;
4Department of Histology, University of Medicine and Pharmacy of Craiova, Craiova, Romania;
5Department of Research Methodology, University of Medicine and Pharmacy of Craiova, Romania;
6Faculty of Medicine, University of Southampton, Southampton SO17 1BJ, UK;
7Department of Clinical Neurosciences, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania

bogdan.catalin@yahoo.co.uk

Aims. Aquaporin-4 (AQP4) is the most abundant water channel in the brain, and its inhibition has been showed to reduce oedema after focal ischemia in imaging studies. Here, we aimed to evaluate, the histopathological effects of a single dose of AQP4 inhibitor administered after medial cerebral artery occlusion (MCAO).

Methods. Using a rat model of non-reperfusion ischemia, we have investigated vascular densities, albumin extravasation, gliosis and apoptosis at 3 and 7 days after MCAO.

Results. Inhibiting AQP4 channels significantly reduced oedema, glial scar, albumin effusion, and apoptosis, at both 3 and 7 days after MCAO. The area of GFAP-positive gliotic rim decreased, and 3D fractal analysis of astrocytic processes revealed a less complex architecture, possibly indicating water accumulating in the cytoplasm. Evaluation of the blood vessels revealed thicker basement membranes colocalizing with exudate albumin in the treated animals, suggesting that inhibition of AQP4 blocks fluid flow towards the parenchyma in the paravascular drainage pathways of the interstitial fluid.

Conclusions. These findings suggest that a single dose of an AQP4 inhibitor can reduce brain oedema, even if administered after the onset of ischemia, and AQP4 agonists/antagonists might be effective modulators of the paravascular drainage flow.

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REGIONAL MINI SYMPOSIUM

Moderators: Emel Ulupinar (Istanbul, TR), Aleksandra Isakovic (Belgrade, RS), Ana-Maria Zagrean (Bucharest, RO)

TOOLS FOR ANALYZING GLIA IN NEURODEGENERATIVE DISEASES

Bilal E. Kerman[1], Sibel Cimen Yetis[2], Abdulkerim Capar[3], Esref Celik[1], İlayda Aydinli[1], Emre Vatandaslar[1], Dunja Bijelic[4], Andrej Korenic[4], Dursun A. Ekinci[3], Gizem Dursun[5], Umut E. Ayten[2], Milena Milosevis[4], Lidija Radenovic[4], Pavle Andjus[4], Ufuk Ozkaya[5], B. Ugur Toreyin[3]

1Istanbul Medipol University, Istanbul, Turkey, 2Yildiz Technical University, Istanbul, Turkey, 3Istanbul Technical University, Istanbul, Turkey, 4University of Belgrade, Belgrade, Serbia, 5Suleyman Demirel University, Isparta, Turkey

bekerman@medipol.edu.tr

Aim: Glial cells are essential for a healthy nervous system. Myelin produced by oligodendrocytes accelerates impulse propagation and supports neuronal survival. Astrocytes contribute to formation of a privileged environment within the central nervous system. Thus, neuroglial dysfunction leads to many neurodegenerative diseases. For example, demyelination via immune attack is the culprit of multiple sclerosis (MS). Astrocytes can rescue degenerating amyotrophic lateral sclerosis (ALS) motor neurons. Our goal is to develop computer software to facilitate analysis of the glia to better asses the disease phenotypes and develop therapies.

Methods: Astrocytes' respond to immunoglobulins isolated from ALS patients differs from their response to control immunoglobulins. In this study, real-time images of astrocytes were recorded and calcium dye intensity variation over time was extracted using various methods. In addition, existing and a custom machine learning algorithms were compared in myelin classification from fluorescent microscopy images. Finally, interactome analysis, which combines gene expression and proteome methodologies, was developed to identify genes involved in MS.

Results and Conclusions: Currently, we are evaluating different segmentation strategies to accurately classify astrocytes in time series images and will present their assessments. Our custom convoluted neural network and Boosted Tree algorithms performed at over 98% accuracy for myelin classification. A myelin quantification workflow will be presented. The interactome analysis yielded novel genes that are likely to be linked to MS. An example gene will be discussed in animal models and in MS patients.

Acknowledgments: This study was supported by H2020 MSCA RISE project 778405 "AUTOIGG", TUBITAK and IMU.

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Room Baltic

SYMPOSIUM 43

REGIONAL MINI SYMPOSIUM

Moderators: Emel Ulupinar (Istanbul, TR), Aleksandra Isakovic (Belgrade, RS), Ana-Maria Zagrean (Bucharest, RO)

METAL DYSHOMEOSTASIS AND OXIDATIVE STRESS IN TAUOPATHIES

Papanikolopoulou Katerina, Turin Luca and Skoulakis Efthimios

BSRC Alexander Fleming, Neuroscience Division, Vari, Greece

papanikolopoulou@fleming.gr

There is an emerging link between the accumulation of metals in the brain and abnormal Tau pathology in a number of neurodegenerative disorders, such as Alzheimer's disease (AD). Studies have demonstrated that metals can regulate Tau phosphorylation and can induce the aggregation of hyperphosphorylated Tau, possibly through a direct interaction via a putative metal binding motif in the Tau protein. Our work provides evidence supporting a critical Tau:metal interaction that may impact Tau-associated neuronal toxicity and dysfunction. Gradual loss of metal binding properties of Tau in the well established Drosophila Tauopathy model leads to increased tolerance to oxidative stress, reduced aggregate formation and improved cognitive performance. As metal ion chelators move towards clinical translation, it is imperative that we understand the intersection between metals and Tau in neurodegeneration.

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Moderators: Emel Ulupinar (Istanbul, TR), Aleksandra Isakovic (Belgrade, RS), Ana-Maria Zagrean (Bucharest, RO)

CATHEPSIN X AS A POTENTIAL THERAPEUTIC TARGET FOR TREATMENT OF PARKINSON'S DISEASE

Anja Pišlar[1] Biljana Božič[2], Nace Zidar[1] Larisa Tratnjek[3], Gordana Glavan[4], Marko Živin[3], Janko Kos[1,5]

1Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia, 2Faculty of Biology, University of Belgrade, Belgrade, Serbia, 3Medical Faculty, University of Ljubljana, Ljubljana, Slovenia, 4Biotechnical Faculty, University of Ljubljana, Ljubljana, Slovenia, 5Jožef Stefan Institute, Ljubljana, Slovenia

najbiljana@yahoo.com

Neuroinflammation is closely implicated in the pathogenesis of neurodegenerative disorders, such as Parkinson's disease (PD), where the hallmark of neuroinflammation is activated microglia. Microglia-derived lysosomal cathepsins, including cathepsin X, are increasingly recognized as important mediators of the inflammation-induced neruodegeneration. Recent study revealed that up-regulated expression and activity of microglial cathepsin X as wells as increased release of cathepsin X after lipopolysaccharide (LPS) stimulation leads to microglia activation-mediated neurodegeneration. Cathepsin X inhibitor caused neuroprotection via its suppression of microglia activation. Moreover, the immunomodulatory role of cathepsin X has been also shown in microglial co-activation, where cathepsin X inhibition proved to diminish increased neuroinflammation by LPS and poly(IC) co-stimulation. Our recent study revealed that LPS also induced the expression and upregulated enzymatic activity of cathepsin X in brain regions observed in in vivo models of PD, with a preference cathepsin X upregulation in microglia cells and astrocytes in lesioned striatum. Taken together, these findings propose the potential function of microglial cathepsin X in inflammation-induced neurodegeneration. Knowing the involvement of cathepsin X in the neurodegenerative processes represent a step towards the development of new molecules for the treatment of neurodegenerative diseases.

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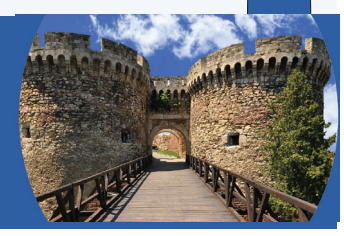

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Room Mediterranean

Special Interest Symposium I

Tinnitus, an interdisciplinary puzzle: new insights on etiology, pathophysiology, diagnostics and therapy

Organizer: Tijana Bojić (Belgrade, RS)

NATURE VERSUS NURTURE: GENETIC CONSIDERATIONS IN THE DEVELOPMENT OF TINNITUS

Trpchevska, N.[1], Zhou, Y.[1], Krebs, K.[2], Milani, L.[2], Lauschke, V.M.[1], Cederroth, C.R.[1]

1 Karolinska Institutet, Department of Physiology and Pharmacology, Stockholm, Sweden;
2 Estonian Genome Center, University of Tartu, Tartu, Estonia

christopher.cederroth@ki.se

Aims: Tinnitus is the most frequent phantom sensation, affecting 70 million individuals in Europe with highly unmet clinical needs. While tinnitus has been thought to derive mainly from environmental factors, we evidenced a significant contribution of genetics in twins and adoptees. Here, we used a pharmacological approach in which we searched for variants in genes coding for drug targets known to cause tinnitus as a side effect.

Methods: We performed an analysis of the genetic landscape of the genes encoding 22 proteins known as targets of drugs causing tinnitus as a side-effect (Elgoyhen et al., 2012, 2014) using freely available human sequencing data of 138,632 individuals provided by the Genome Aggregation Database (GnomAD). Variants were considered deleterious when they resulted in frameshifts, premature stop-codons, loss of the start codons or disruption of splice donor or acceptor sites. Missense variants were tested using 20 algorithms to test their likelihood of altering protein function (defined as deleterious) via ANNOVAR. Selected variants were tested for their association with clinically significant tinnitus (H93.1) using the Estonian Biobank (n=2,757 cases and 32,884 controls).

Results: Using orthogonal computational functionality predictors, we identified 42 variants with functional impact (MAF > 0.1%) in the European population. We found two missense variants with a significant association with clinically significant tinnitus.

Conclusions: Our findings strongly support the notion that genetic factors impact on the development of tinnitus. We propose a molecular basis for tinnitus and provide a new understanding on the mechanism leading to this neurological disorder.

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Special Interest Symposium I

Tinnitus, an interdisciplinary puzzle: new insights on etiology, pathophysiology, diagnostics and therapy

Organizer: Tijana Bojić (Belgrade, RS)

CENTRAL MECHANISMS OF CHRONIC SUBJECTIVE TINNITUS AND IN SILICO PROPOSALS FOR TINNITUS TREATMENT

Tijana Bojić

Laboratory for radiobiology and molecular genetics -080, Institute of Nuclear sciences Vinča University of Belgrade

tijanabojic@vinca.rs

The phantom limb perception is often used as an analogy to the pathophysiology of tinnitus. Damage in the cochlea leads to a frequency-specific decrease in the output from the cochlear nerve. An upregulation of activity in the central auditory pathway is a compensatory effort to counteract the lack of signals in the particular frequency area. This effort increases the gain, falsely leading to the perception of a non-existing sound and possibly accompanying hyperacusis. In addition to the auditory pathway, tinnitus shares non-auditory networks (perception, salience, distress, and memory). Such networks, may maintain, in absence of the initial "tinnitus-initiator". This activity becomes a conscious percept upon connection to a larger brain networks located in the frontal and parietal areas of cortex, such as "self-awareness" and "salience network." The latter network intersects with the central autonomic control system and affects the limbic-auditory and somatosensory interaction indispensable for consciously maintaining the phantom perception (Figures 1, 2). This perception may associate with distress, simultaneously co-activating non-specific distress networks located in the anterior cingulate cortex, anterior insula and amygdala. At the same time, it is proposed that memory mechanisms may reinforce and maintain the awareness of the phantom percept. We propose novel hybrid electromagnetic and pharmacological modulation of central brain networks as the promising approach in the treatment of tinnitus (Figure 3).

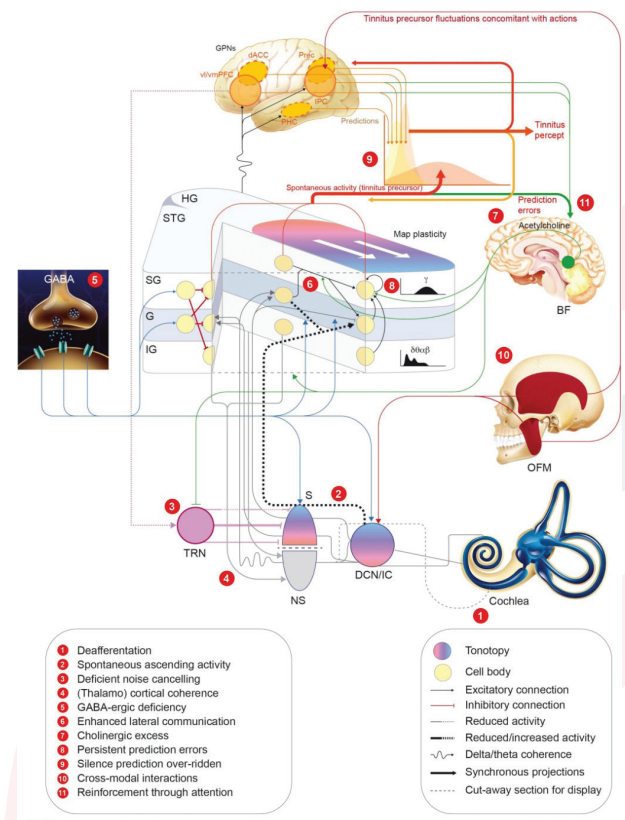

Figure 1. Potential mechanisms involved in tinnitus pathophysiology. GPNs, global perceptual networks; vl/vmPFC, ventrolateral/ventromedial prefrontal cortex; dACC, dorsal anterior cingulate cortex; Prec., precuneus; IPC, inferior parietal cortex; PHC, parahippocampal cortex; HG, Heschl's gyrus; STG, superior temporal gyrus; SG/G/IG, supragranular/granular/infragranular neuronal layers; BF, basal forebrain; OFM, orofacial movements; S, specific (lemniscal) auditory thalamus; TRN, thalamic reticular nucleus; NS, non-specific auditory thalamus; DCN, dorsal cochlear nucleus; IC, inferior colliculus.

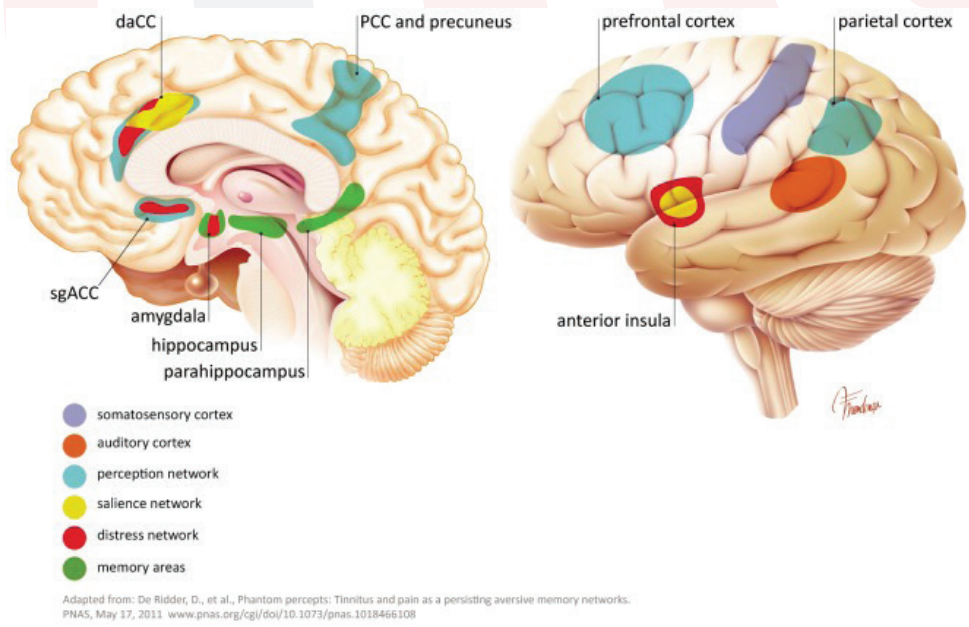

Figure 2. Some extra auditory regions involved in tinnitus pathophysiologyFigure

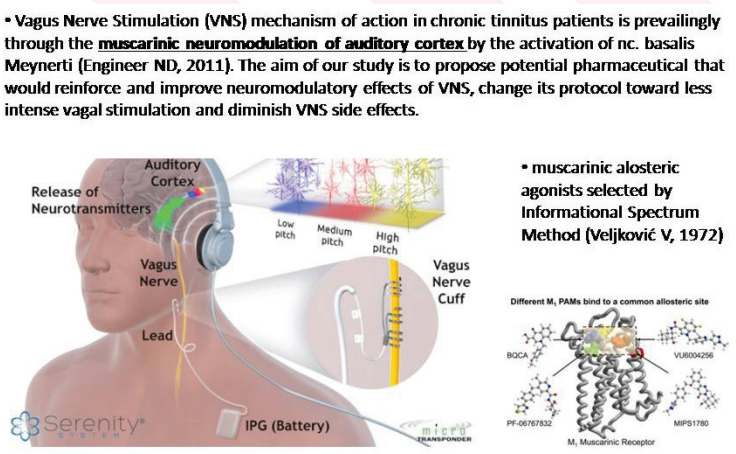

Figure 3. Model of hybrid neuromodulatory approach for the treatment of tinnitus

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Special Interest Symposium I

Tinnitus, an interdisciplinary puzzle: new insights on etiology, pathophysiology, diagnostics and therapy

Organizer: Tijana Bojić (Belgrade, RS)

EVIDENCE FOR BIOLOGICAL MARKERS IN TINNITUS: A SYSTEMATIC REVIEW

Haúla Haider, Diogo Ribeiro, Asma Elarbed, Agnieszka J Szczepek, Maria Martins, Nuno Trigueiros, Luís Borrego, Ana Papoila, Helena Caria, João Paço and Derek J Hoare

ENT Department Hospital Cuf Infante Santo, Lisbon, Portugal

hfhaider@gmail.com

Subjective tinnitus is a phantom sound heard only by the affected person and may be a symptom of various diseases. Currently, diagnosis and monitoring of tinnitus are based on subjective audiometric and psychometric measurements, and there are no objective methods. The aim of this review was to synthesise the evidence for the existence and clinical usefulness of biomarkers of the development or severity of tinnitus.

We conducted a systematic search of several databases. The initial searches were complemented by scanning reference lists from relevant systematic reviews and the included primary studies; citation searching of the included primary studies using Web of Science, and hand searching the last 6 months of key otology journals. All systematic review stages were carried out by at least two authors. Forty-six records were included in the review and were categorized according to the biological variable measured. There was no evidence for an association between tinnitus and thyroid function, glucose blood level, sedimentation velocity, C-reactive Protein, or unspecific serum Immunoglobulins. The results showed conflicting evidence for the association between tinnitus and full blood count, lipid profile, oxidative stress, vitamins, neurotrophic factors and inorganic ions. However, there was a negative correlation between steroid levels and tinnitus. Neurotransmitters as tinnitus biomarkers are a promising line of investigation. Biological markers may provide an easier means for determining the diagnosis and prognosis of tinnitus, as well as a measure of treatment effectiveness. However, larger studies, with stricter exclusion criteria and powerful harmonized methodological design are needed.

Protocol published on PROSPERO (CRD42017070998).

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Tinnitus, an interdisciplinary puzzle: new insights on etiology, pathophysiology, diagnostics and therapy

Organizer: Tijana Bojić (Belgrade, RS)

MOMENTARY ASSESSMENT OF TINNITUS - HOW SMART MOBILE APPLICATIONS ADVANCE OUR UNDERSTANDING OF THE NEUROSCIENCE OF TINNITUS

Jorge Piano Simões[1], Rüdiger Pryss[2],Johannes Schobel[2], Winfried Schlee[1]

1University of Regensburg, Regensburg, Germany;

2University of Ulm, Ulm, Germany

jorge.simoes@ukr.de

Tinnitus is a condition associated with a continuous noise in the ears or head and can arise from many different medical disorders. The perception of tinnitus can vary within and between days. In the recent years, Ecological Momentary Assessments of tinnitus have been used to investigate these tinnitus variations during the daily life of the patients. In the last five years, several independent studies have used Ecological Momentary Assessment to assess tinnitus. With this chapter, we want to review the current state of this research.

All the EMA studies revealed a considerable variability of tinnitus loudness and tinnitus distress. It has been found that emotional states and emotional dynamics, the subjectively perceived stress level and the time of the day exert influence on the tinnitus variability. In summary, the EMA method revealed a good potential to improve our scientific understanding of tinnitus. Furthermore, it also showed that it can be used to understand the individual differences of tinnitus - and may even be used as a tool for individualized diagnostic and treatment. We conclude, that the results of the EMA studies can lead to improvements of existing research methods in the field of tinnitus.

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Special Interest Symposium II

Circadian and redox regulation in the development and potential treatment of substance addiction

Organizer: Rozi Andretić Waldowski (Rijeka, HR) and Ana Filošević (Rijeka, HR)

REDOX REGULATION OF PSYCHOSTIMULANT-INDUCED BEHAVIORS IN D. MELANOGASTER

Ana Filošević, Željko Agić, Franka Rigo, Rozi Adretić Waldowski

University of Rijeka, Department of biotechnology, Laboratory for behavior genetics, Rijeka, Croatia

ana.filosevic@biotech.uniri.hr

Recent evidence suggests that redox (reduction-oxidation) balance modulates different forms of neuronal plasticity. Several circadian genes modulate development of locomotor sensitization, a type of neuronal plasticity, that develops after repeated administrations of cocaine. External factors, such as psychostimulant administration can perturb redox balance. Here we test: first, that redox balance regulates development of locomotor sensitization after cocaine administration in laboratory model organism, *Drosophila melanogaster*, and second, that the activity of antioxidant enzymes depends on circadian mutant background.

Drosophila melanogaster develops locomotor sensitization to volatilized cocaine when administrations are given 6 hrs. apart. Locomotor sensitization is abolished in circadian mutant strains: per^{01}, cyc^{01}, Clk^{Jrk}, but is preserved in tim^{01}*flies*. Pre-feeding *wild-type* (*wt*) flies antioxidants (querctine or tyrosol) or pro-oxidants (hydrogen or paraquat) likewise abolishes development of locomotor sensitization. We measured the baseline activity of catalase (CAT) and superoxide dismutase (SOD) in the heads of *wt* flies and per^{01}, tim^{01}, cyc^{01} and Clk^{Jrk} at two time points during the day: 09:00 and 15:00 hours and compared that *to* CAT and SOD activity of flies collected 30 min after repeated cocaine administration at 15:00 hrs. We find that CAT and SOD activity is genotype-dependent, and that CAT and SOD activity change in genotype-dependent manner after cocaine exposure.

These results suggest that changed redox balance in CNS of *wt* flies after acute and repeated COC exposures could influence neuronal plasticity. Furthermore, behavioral phenotype in response to cocaine has a biochemical correlate in the form of activity of antioxidant enzymes in circadian mutants.

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Organizer: Rozi Andretić Waldowski (Rijeka, HR) and Ana Filošević (Rijeka, HR)

CIRCADIAN SYSTEM AND OXIDATIVE STRESS RESISTANCE IN *DROSOPHILA MELANOGASTER*

Serge Birman

Genes Circuits Rhythms and Neuropathology group, Brain Plasticity unit, CNRS, PSL Research University, ESPCI Paris, France

serge.birman@espci.fr

In many organisms, oxidative stress and aging have a negative impact on the circadian system, resulting in various physiological and behavioural defects. Conversely, the loss or weakening of the clock decreases resistance to oxidative stress and can reduce lifespan. However, the signalling mechanisms by which endogenous clocks improve stress resistance and life expectancy are not yet well understood. The fruit fly *Drosophila* is widely used to study the circadian system and as a model of aging and neurodegenerative diseases. In previous work, we have studied the effects of genetic or environmental clock disturbances on locomotor decline and longevity in *Drosophila*. We have identified a requirement for the core circadian gene *Clock* in the brain pacemaker neurons that express the neuropeptide pigment-dispersing factor (PDF) to maintain the integrity of specific dopaminergic neurons and avoid premature locomotor aging induced by PDF receptor signalling (1). We have also recently examined the protective action of vertebrate pituitary adenylate cyclase-activating polypeptide (PACAP) against the environmental oxidative stressor paraquat in the *Drosophila* nervous system. The application of PACAP has a powerful neuroprotective effect in adult flies but only in the presence of PDF or its receptor (2). These and further studies suggest that oxidative stress resistance and aging in *Drosophila* are partly controlled by a circadian-independent influence of specific clock genes in the central nervous system, which involves a small number of interconnected neurons.

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Special Interest Symposium II

Circadian and redox regulation in the development and potential treatment of substance addiction

Organizer: Rozi Andretić Waldowski (Rijeka, HR) and Ana Filošević (Rijeka, HR)

A SURVEY OF HOW THE CIRCADIAN CLOCK MAY IMPACT ADDICTION BEHAVIOUR

Martha Merrow
LMU Munich, Munich, Germany

merrow@lmu.de

Circadian clocks govern the timing of behaviour and physiology throughout the body. One of the most interesting demonstrations of this is how individuals synchronise (entrain) to the external light dark cycle (zeitgeber), a process which leads to a distinct sleep-wake schedule. Interindividual variation leads to a distribution of chronotypes. When a late chronotype adheres to a conventional social schedule (school or work times) they accumulate a chronic sleep debt. These individuals, in addition to carrying metabolic decrements, are more likely to become addicted to nicotine and to be depressed. If living against the clock leads to addiction, are there ways that we can use the circadian clock in order to prevent or possibly treat it? I will present evidence that using zeitgeber cycles in a simple model of protein aggregation actively changes cellular processes leading to drastic alterations. The implication is that it is not only the circadian clock but its synchronisation – a process that we can actively participate in - that is important for psychosocial health.

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Special Interest Symposium II

Circadian and redox regulation in the development and potential treatment of substance addiction

Organizer: Rozi Andretić Waldowski (Rijeka, HR) and Ana Filošević (Rijeka, HR)

NUTRITIONAL THERAPY IN SUBSTANCE USE DISORDER: IMPROVED MENTAL HEALTH DURING RECOVERY FROM SUBSTANCE USE DISORDER WITH ADJUNCTIVE USE OF A PALATABLE NUTRIENT-RICH DRINK SUPPLEMENT

E. Leigh Gibson, Kendall Jeynes and Meghan Murphy

Departments of Psychology and Life Sciences, Whitelands College, University of Roehampton, London, United Kingdom

l.gibson@roehampton.ac.uk

Aims: Substance and alcohol use disorders (SUD) represent a substantial challenge to economies and societies worldwide. Malnutrition and poor appetite are common in SUD; nutritional deficiencies, and chronic hunger, may enhance the drive to consume addictive substances, through effects on neuroendocrine regulation of appetite (Jeynes & Gibson, 2017).

Methods: An open randomised controlled pilot study was conducted to test whether adjunctive nutritional therapy could improve outcomes during recovery from SUD. SUD participants (n=21) were recruited from three recovery support centres in London (Blenheim CDP), and were randomly assigned to a drink supplement 'Drink Group' or usual treatment 'Control Group', stratified by treatment centre. The drink contained dairy (energy and calcium), fibre, 21 g protein, iron and B-complex vitamins, in a palatable form, and was consumed once per day for up to 3 months. Outcomes, assessed at baseline and monthly, included mental and physical health (SF-36v2, QualityMetric Inc.), dietary and appetite assessments, and body composition. Due to drop-out, an intention-to-treat analysis was used (Drink Group n=11; Control Group n=6).

Results: Mental health (SF36v2 norm-based scoring; overall and vitality subscale) was significantly improved in the Drink Group vs. Control. Appetite also tended to improve vs. Control, but no other significant group differences were found. Self-reported nutritional risk factors, as well as anxiety and depression (HADS), improved equally in both groups, suggesting additional benefits of usual treatment.

Conclusions: Despite the small sample in this study, the improvement in mental health supports further investigation of use of nutritional therapy to improve SUD treatment outcomes.

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NANO SYMPOSIUM I

BRAIN NETWORKS IN EPILEPTIC SEIZURES - INSIGHTS FROM ZEBRAFISH

Richard Rosch

King's College London, London, United Kingdom

roschkoenig@gmail.com

Zebrafish are a vertebrate animal model that has recently gained interest from the epilepsy research community. These vertebrate animal models are small, are amenable to genetic modification, and with recent advances in light sheet microscopy we can now perform functional neuroimaging of the whole larval zebrafish brain at single cell resolution. At the same time, understanding these complex datasets and relating them to the pathobiology remains challenging.

In this study we image larval zebrafish at six days post-fertilisation with a genetically encoded calcium sensor (GCaMP6s) using whole-brain light sheet imaging. From these time series data we identify the changing neuronal network composition as seizure dynamics are established in the larval brain, identifying key network hubs and statistical signatures of seizures in these zebrafish. In a second step we show correspondence of some of these features in the larval zebrafish brain with networks derived from seizures in patients that were recorded using stereotactically recorded EEG.

Our study indicates the potential of this new model to allow a detailed, integrated understanding of epileptic seizures across multiple scales. With optical access to the entire zebrafish brain, we can image at scale, whilst retaining a spatial resolution that is impossible to achieve in human subjects. Novel computational tools allow us to then identify the corresponding phenotypic features between zebrafish and patients living with epilepsy as illustrated here.

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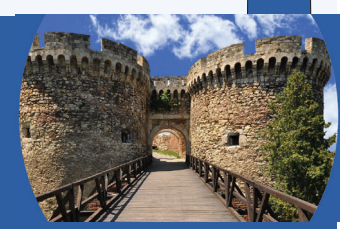

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NANO SYMPOSIUM I

MAGNESIUM AND TRANSIENT RECEPTOR POTENTIAL CHANNELS IN PAIN

D. Srebro, S. Vuckovic, M. Prostran

Department of Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia;

srebrodragana1@gmail.com

Aim of Investigation: Beside antinociceptive activity, magnesium may also have local pronociceptive action. This study aimed to asses the pro-/anti-nociceptive effect and mechanism of action of intraplantar (i.pl.) administration of magnesium sulfate (MS) in rats.

Materials and methods: In male Wistar rats the paw withdrawal threshold to mechanical stimuli was evaluated by the electronic von Frey test. MS was administered i.pl. with/without tested antagonist of the transient receptor potential ion channels ankyrin type (TRPA1) or vanilloid types (TRPV1 and TRPV4) or acid-sensing ion channels (ASIC).

Results: MS at doses of 0.5 - 6.2 mg/paw (i.pl.) induced local and dose-dependent mechanical hyperalgesia. Isotonic MS (6.2 mg/paw) induced mechanical hyperalgesia that lasted at least six hours. Isotonic pH-adjusted (7.4) MS-induced mechanical hyperalgesia was reduced by co-injection of HC-030031, a selective TRPA1 antagonist (140 nmol/paw), capsazepine, a selective TRPV1 antagonist (500 pmol/paw) or RN-1734, a selective TRPV4 antagonist (6.2 µmol/paw). Amiloride hydrochloride, a non-selective ASIC inhibitor (7.55 µmol/paw) did not change MS-induced hyperalgesia.

Conclusion: Local injection of isotonic pH-adjusted solution of MS (6.2%; pH 7.4) induces local peripheral pain to mechanical stimuli. This effect is mediated via activation of TRPA1, TRPV1 and TRPV4 receptors probably in primary afferent fibers.

This work was supported by the Ministry of Education, Science and Technological Development of Serbia (Grant No. 175023).

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NANO SYMPOSIUM I

POTASSIUM CHANNELS ARE IMPORTANT PLAYERS IN MICROGLIAL CELLS

Alexandru-Florian Deftu[1], Ruxandra-Elena Anton[1], Melania Bica-Popi[1], Christophe Gattlen[2], Isabelle Decosterd[2], Marc-René Suter[2], Violeta Ristoiu[1]

1Department of Anatomy, Animal Physiology and Biophysics, Faculty of Biology, University of Bucharest, Romania; 2Pain Center, Department of Anesthesiology, Lausanne University Hospital (CHUV) and Faculty of biology and medicine (FBM) University of Lausanne (UNIL), Switzerland

alex.deftu@bio.unibuc.ro

Aims: Microglial cells are activated following nerve injury and are important members in the nociceptive pathways. The aim of this project was to investigate how potassium currents in microglial cells are altered after spared nerve injury (SNI) and how the microglial migration and proliferation are changed due to these ion channels.

Methods: Adult male CX3CR1-GFP transgenic mice undergone a SNI surgery, were sacrificed after 2days and lumbar spinal cord was incubated in the presence of papain for 30min at 30°C. Microglia were kept in culture until patch-clamp experiments or cultured on 8µm inserts for cell migration.

Results: Two days after SNI the potassium currents showed an increase in the current density of -91.04 ± 67.55 pA/pF, n=51, at a step of -160mV, compared with -43.86 ± 28.36 pA/pF, n=21, in naive conditions. The current density decreased at -78.60 ± 45.31 pA/pF, n=7, at a step of -160mV, when using 3.2µM $Ba(OH)_2$, illustrating the contribution of Kir2 ion channels. The IV-curves recorded showed different kinetics after 0.05mM CsCl with a current density of -12.96 ± 5.48 pA/pF, n=14, at a step of -160mV. Our further experiments showed that the proliferation and the migration of microglial cells decreased after the treatment with ML133, a specific inhibitor of Kir2.

Conclusions: Cultured microglia expresses potassium currents which increases two days after the SNI pain model. The experiments with cesium and barium indicate that the predominant channels are Kir2. The specific inhibitor ML133 is decreasing the proliferation and migration rate mediated by Kir2 channels.

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Room Atlantic 1

NANO SYMPOSIUM I

SELECTIVE INHIBITION OF $CA_V3.2$ CHANNELS REVERSES HYPEREXCITABILITY OF PERIPHERAL NOCICEPTORS AND ALLEVIATES POSTSURGICAL PAIN

Sonja Lj. Joksimovic[1], Srdjan M. Joksimovic[1], Vesna Tesic[1], Agustin Garcia Caballero[2], Simon Feseha[1], Vesna Jevtovic-Todorovic[1], Gerald W. Zamponi[2], Slobodan M. Todorovic[1]

1Department of Anesthesiology, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA;
2Department of Physiology and Pharmacology, Cumming School of Medicine, University of Calgary, Canada

sonja.joksimovic@ucdenver.edu

Introduction: Pain-sensing sensory neurons of the dorsal root ganglion (DRG) become sensitized or hyperexcitable in response to surgically induced peripheral tissue injury. We investigated the potential role and molecular mechanisms of nociceptive ion channel dysregulation in acute pain resulting from skin and soft tissue incision.

Methods: We used selective pharmacology, electrophysiology, immunocytochemistry and mouse genetics to link changes in current densities arising from the $Ca_V3.2$ isoform of T-type calcium channels (T-channels) to nociceptive sensitization using a clinically relevant rodent model of skin and deep tissue incision. Surgical incision of the plantar surface of the hind paw was performed in Sprague-Dawley rats and C57BL/6J wild-type (WT) and $Ca_V3.2$ knock-out (KO) mice. To assess the role of $Ca_V3.2$ channels in incisional pain, after intrathecal application of USP5-shRNA, an important regulator of $Ca_V3.2$ channel ubiquitination, hind paw responses to mechanical stimulus were measured.

Results: Increase in T-currents in small DRG neurons has been detected after surgery. After surgery DRG neurons exhibited increase in high-frequency firing comparing to the sham group. Pan-selective T-channel blocker (TTA-P2) reduced the number and frequency of action potentials in sensory neurons after incision. Immunocytochemistry confirmed that surgical incision increases membrane fraction of $Ca_V3.2$ channels. Mechanical hyperalgesia was significantly reduced in global $Ca_V3.2$ KO, versus WT mice after incision, while selective knock-down of USP5 had the same effect in incised rats.

Conclusion: Our study identifies $Ca_V3.2$ channels as a novel target for treating perioperative pain that may greatly decrease the need for narcotics and potential for drug abuse.

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NANO SYMPOSIUM I

EFFICACY OF EXTRACELLULAR VESICLES IN EXPERIMENTAL MODELS OF ISCHEMIC STROKE

Roxana Surugiu[1], Danut-Adrian Dumbrava[1], Andrei Gresita[1], Leonard Pinoseanu[1], Madalina Aldea[1], Dirk Hermann[3,4], Aurel Popa-Wagner[1,2]

1Neurobiology of Aging Group, University of Medicine and Pharmacy, Craiova, Romania;
2Griffith University School of Medicine, Gold Coast Campus, QLD 4222, Australia;
3Department of Neurology, Chair of Vascular Neurology and Dementia, University of Medicine Essen, Germany;
4Department of Neurology, University Hospital Essen, Germany;

aurel.popa-wagner@geriatrics-healthyageing.com

Being one of the leading causes of death and long-term disabilities and with only a few treatment options, stroke therapies is a research field where urgent studies on animal models are required in order to start the human clinical trials. Ischemic stroke is a leading cause of death and long-term disability in industrialized countries, with thrombolysis and interventional vascular recanalization being the only treatments available. To improve brain remodelling and plasticity, and to bypass limitations of endogenous neurogenesis following ischemic stroke, a variety of approaches started to focus on the transplantation of neural progenitor cells (NPC) or somatic stem cell entities, such as mesenchymal stem cells (MSCs). It was observed that systemic NPC delivery induces profound brain tissue remodelling, reflected by reduced secondary neurodegeneration, reduced neuroinflammation, reduced astrogliosis and reduced microglial activation, that was associated with functional neurological recovery. Remarkably, it turned out that systemic intravenous administration of adult NPCs was more effective than their intracerebral transplantation; only systemic administration effectively resulted in the stabilization of blood-brain barrier integrity. In this ongoing study we examined whether MSC-derived extracellular vesicles (3 x 0.05 or 0.5 IU/ kg) protect against focal cerebral ischemia, when delivered i.v. at 24 hours, 72 hours and 120 hours after distal MCAO in aged rats (18-24 months) and day one, three, seven and fourteen in young animals. Deficits in motor coordination and spatial memory were observed in ischemic vehicle (normal saline)-treated rats, which were attenuated by MSC-derived extracellular vesicles. Extracellular vesicle delivery went along with significantly decreased infarct volume, reduced microglial activation/ macrophage invasion, reduced astroglial scar formation, increased neurogenesis and increased angiogenesis. Our data provide further evidence supporting the efficacy of mesenchymal stem cells as new approaches in cell therapy for stroke patients.

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Room Atlantic 1

NANO SYMPOSIUM I

NON-INVASIVE ELECTRICAL STIMULATION MAY ALLEVIATE SYMPTOMS OF PARKINSON DISEASE

Özgür Öztop Çakmak

Koç University Hospital, Istanbul, Turkey

Ooztop@ku.edu.tr

Parkinson's disease (PD) is a health care problem and a progressive neurodegenerative disorder. An estimated 7 to 10 million people are affected by the disease worldwide, with future projections of an increase incidence. The pathophysiology of PD is still unclear, but loss of dopamine-producing neurons have been implicated in the basal ganglia, the region that plays a role in the control of voluntary movements, leading to the motor symptoms of PD.

Clinical manifestations include motor symptoms such as bradykinesia, postural instability, rigidity and tremor as well as non-motor symptoms such as cognitive dysfunction, dementia, sleep disturbances, and autonomic dysfunction. Treatment options comprise pharmacologic, non-pharmacologic and surgical therapy. Since the clinical presentation of disease varies between patients, management of PD should be individualized. Medications include dopaminergic agents and levodopa. In advanced disease, management of patients may become challenging due to fluctuating response to medical treatment, referred to as motor fluctuations.

Deep brain stimulation (DBS) is a neurosurgical procedure performed in addition to medical treatment for advanced PD to increase patients' quality of life. Bilateral DBS has been shown to improve motor functions in selected patients with advanced PD and motor fluctuations, but like every surgical procedure, it has an increased risk of complications such as infection and hemorrhage.

Electrostimulation of the Intrinsic auricular muscle zones (IAMZ), which is much less invasive than DBS, may contribute to the motor regulation of the centers involved in modulation of movement. We aimed to investigate clinical responses of PD patients to the IAMZ stimulation.

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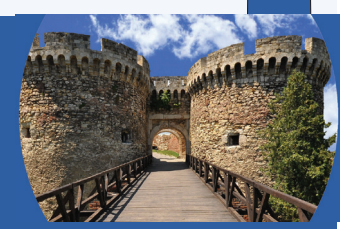

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Room Atlantic 2

NANO SYMPOSIUM II

ISCHEMIA/REPERFUSION BRAIN INJURY AND DEHYDROEPIANDROSTERONE MODULATE OXIDATIVE STRESS AND INFLAMMATORY RESPONSE INDICATORS IN PREFRONTAL CORTEX

Drakulić Dunja[1]*, Veljković Filip[2], Pejić Snežana[1], Todorović Ana[1], Zarić Marina[1], Mitrović Nataša[1], Grković Ivana[1], Guševac Stojanović Ivana[1], Dragić Milorad[3], Martinović Jelena[1]

1University of Belgrade - VINČA Institute of Nuclear Sciences, Department of Molecular Biology and Endocrinology, Belgrade, Republic of Serbia;
2University of Belgrade - VINČA Institute of Nuclear Sciences, Department of physical chemistry, Belgrade, Republic of Serbia;
3University of Belgrade - Faculty of Biology, Department of General Physiology and Biophysics, Belgrade, Republic of Serbia

drakulic@vin.bg.ac.rs

Cellular and tissue damage following ischemia/reperfusion brain injury arise due to sudden reduction of cerebral blood flow and disturbance in oxygen and nutrient supply accompanied by abrupt vascular restoration, reoxygenation and rehabilitation of nutrients transport. Several therapeutic agents, including dehydroepiandrosterone (DHEA), have been proposed to protect brain from these deleterious outcomes. However, DHEA effect on oxidative stress indicators (pro-oxidant/anti-oxidant balance (PAB), 4-hydroxynonenal (4HNE), malondialdehide (MDA), and advanced oxidation protein products (AOPP)), and inflammatory response (ecto-5'-nucleotidase (eN)), not only in pathological but also in physiological conditions are still ambivalent. In current experimental setup, adult male Wistar rats were subjected to a single dose of vehicle or DHEA (20 mg/kg, i.p.) 4 h following sham operation or bilateral common carotid artery occlusion lasting 15 min. All biochemical analyses were performed on precortical samples obtained 24 h following both surgical procedures, in order to compare the levels of examined markers between groups. The results show that in comparison to vehicle treatment, DHEA after sham operation was insufficient to induce any change of all investigated parameters. Following vehicle treatment, a significant post-ischemic increment of oxidative stress and inflammatory response indicators was detected. In pathological condition after DHEA treatment, MDA and 4HNE were still increased, while the levels of PAB, AOPP and eN were similar to the one observed in sham operated animals. Overall, presented data indicate that DHEA may be valuable in preventing some of oxidative stress-related and inflammatory-mediated cellular processes associated with ischemia/reperfusion brain injury.

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NANO SYMPOSIUM II

LESSONS LEARNT FROM ALS IGG

Milena Milosevic, Dunja Bijelic, Katarina Milicevic, Pavle Andjus

Center for Laser Microscopy, Faculty of Biology, University of Belgrade, Serbia

milmi@bio.bg.ac.rs

Amyotrophic lateral sclerosis (ALS) is a complex neurodegenerative disorder, where both upper and lower motor neurons selectively degenerate. Lately, clear evidence immerged about the non-cell autonomous mechanisms, strongly involving glial cells, as well as immune-mediated mechanisms.

We have directed our research towards the effect of IgG purified from the sera of ALS patients on both neuronal and glial cells, with the aim of evaluating the potential of ALS IgG as a specific disease marker. Several imaging approaches were used for this purpose, all involving live monitoring of the acute effect of ALS IgG on the cells of interest.

Vesicle mobility studies revealed enhanced mobility of acidic vesicles in astrocytes treated with ALS IgG. Calcium imaging studies showed several types of responses to ALS IgG, where the major source of calcium in astrocytes was pinpointed to IP3 mediated release from ER. The use of fluorescent genetically encoded indicators of cytosolic peroxide and pH, as well as reactive oxygen species indicators revealed the acute response of BV-2 cells to the fraction of ALS IgG tested, suggesting the potential role of inflammatory humoral factors as possible triggers of the microglial activation, known to occur in the later stages of ALS.

The detailed characterization of the acute responses of different cell types to ALS IgG should lead to stratifying the patient cohort according to state of their humoral immune system. On the other hand, revealing the subtle interactions among different cell types might lead to designing new promising treatments, and lead to personalized medicine.

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NANO SYMPOSIUM II

IL-33/ST2 PATHWAY IN PATHOGENESIS AND SOMATIC COMORBIDITY IN PSYCHOSIS

Milica M. Borovcanin[1], Slavica Minic Janicijevic [1], Ivan Jovanovic [2], Nevena Gajovic [2], Nebojsa N. Arsenijevic [2], Miodrag L. Lukic [2]

1 Department of Psychiatry, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia;
2 Center for Molecular Medicine and Stem Cell Research, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia

milicaborovcanin@yahoo.com

Schizophrenia and treatment of this disorder are often accompanied with metabolic syndrome, cardiovascular issues and higher risk of breast carcinoma was established in female schizophrenia patients. Alterations of the serum level of interleukin-33 (IL-33) and its receptor IL-33R (ST2) were observed in these somatic conditions, but also in neurological disorders and behavioral changes. Consequently, we have investigated the serum level of IL-33 and soluble ST2 (sST2) in different stages of schizophrenia. Levels of IL-33 and sST2 are higher in schizophrenia exacerbation in comparison with controls and patients in remission. The positive correlation of IL-33 with positive symptoms in remission suggests its potential role in underlying mechanisms of psychosis onset and sST2 could have neutralizing properties in the context of excessive IL-33 secretion and also in amelioration of negative symptoms. The positive correlation of Creatine Kinase-MB levels with serum sST2 was established and simultaneously presented higher scores on items equivalent of aggressive behavior suggest that these new inflammatory markers should be considered in additional monitoring of cardiac symptoms that occur without warning in schizophrenia. Further, schizophrenia relapse characterized by an increase in IL-33 may be facilitating factor leading to more frequent occurrence of breast carcinoma in female schizophrenia patients. This initial analysis of new markers of neuroinflammation suggested their involvement in schizophrenia pathophysiology and/or somatic comorbidity.

This work was supported by grants from the Ministry of Science and Technological Development of Republic of Serbia (projects 175103 and 175069) and from the Faculty of Medical Sciences, University of Kragujevac (project JP 12-09 and JP 15-05).

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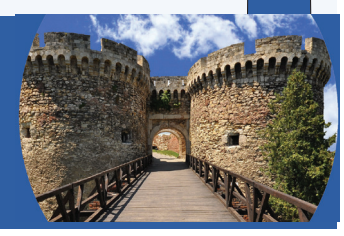

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NANO SYMPOSIUM II

INTERFERON GAMMA MEDIATES MICROGLIA POLARIZATION AND DELAY IN CEREBELLAR GROWTH FOLLOWING CONGENITAL CYTOMEGALOVIRUS INFECTION

Daria Kveštak[1], Vanda Juranić Lisnić[1], Berislav Lisnić[1], Ilija Brizić[1], Jelena Tomac[1], Mijo Golemac[1], Ester Pernjak Pugel[1], Astrid Krmpotić[1], William J. Britt[2] and Stipan Jonjić[1]

1Department of Histology and Embryology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia;
2Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama

daria.kvestak@medri.uniri.hr

Congenital human cytomegalovirus (HCMV) infection is the most common viral cause of long-term neurodevelopmental sequelae, including mental retardation, microcephaly and sensorineural hearing loss. As HCMV does not cross species barrier, we employed a mouse model in which newborn mice are infected intraperitoneally (i.p.) with non-lethal doses of mouse cytomegalovirus (MCMV). Following infection the virus disseminates to the CNS, replicates in the brain parenchyma and causes altered cerebellar development. The pathogenesis of the CNS infection has not been completely clarified and may arise as a result of direct damage of MCMV infected neurons or indirectly secondary to inflammation. Since the initial inflammatory response in the brain is mediated by the activated microglia, the resident immune cells of the CNS, we investigated the impact of MCMV infection on the functional properties of microglia. We observed that MCMV infection induces early activation of microglia towards proinflammatory or M1 phenotype. These cells upregulated both MHC I and MHC II, CD80 and STAT1 expression. Activation of microglia during CMV infection leads to production of proinflammatory cytokine TNF alpha and iNOS. In addition, we performed transctiptomic analysis of microglia isolated from MCMV infected brains. Majority of differentially expressed genes in microglia from MCMV infected mice were those connected with response to interferon gamma, antigen presentation and immune response. We demonstrated that MCMV infection induces dramatic upregulation of MHC II molecules on microglia which can be abolished by neutralization of interferon gamma. Notably, interferon gamma neutralization also normalized altered cerebellar development. These results indicate that interferon gamma is a major component of the inflammatory response that is associated with altered neurodevelopment that follows CMV infection.

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NANO SYMPOSIUM II

EXPRESSION OF GROWTH HORMONE RECEPTOR (GHR) IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

Iva Bozic[1], Katarina Tesovic[1], Marija Janjic[1], Danijela Savic[1], Danijela Laketa[2], Marija Jakovljevic[1], Ana Milosevic[1], Sanja Pekovic[1], Irena Lavrnja[1]

1 Department of Neurobiology, Institute for Biological Research "Sinisa Stankovic", University of Belgrade, Belgrade, Serbia;
2 Department for General Physiology and Biophysics, Faculty of Biology, University of Belgrade, Belgrade, Serbia

iva.bozic@ibiss.bg.ac.rs

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) characterized by inflammation, demyelination, neurodegeneration and gliosis. It is considered as a perplexing multifactorial disease in which the neuroendocrine system plays an important role. Growth hormone (GH) is synthesized and secreted by the somatotroph cells of the anterior pituitary. GH secretion is positively regulated by the hypothalamic factor GHRH and exerts its effects through interaction with the GH receptor (GHR), a member of the class I cytokine receptor family. It was demonstrated that neurons and astrocytes also produce GH and that GHR is widely expressed in the CNS. Nonetheless, it is not known whether expression pattern of GHR changes in the CNS during MS. We investigated GHR expression in the spinal cord during the course of experimental autoimmune encephalomyelitis (EAE), animal model of MS that is broadly used. Our results show that GHR is diminished on mRNA and protein level during EAE. Double immunofluorescence studies demonstrated that GHR is expressed in different cell types in the spinal cord in physiological conditions, including astrocytes and microglia. This expression pattern does not change extensively after the onset of EAE. However, at the peak of disease GHR is absent from astrocytes in the white and grey matter, but still present in microglia, although to a lesser degree. At the end of disease, when the animals have recovered, GHR expression is similar to control conditions. Our results point to complex involvement of GHR in the pathology of EAE.

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NANO SYMPOSIUM III

SYNERGISTIC ANTIGLIOMA ACTION OF LYSOSOMAL MEMBRANE PERMEABILIZATION AND GLYCOLYSIS INHIBITION

Verica Paunović[1], Milica Kosić[1], Katarina Arsikin-Csordas[1], Raymond A. Firestone[2], Biljana Ristić[1], Aleksandar Mirčić[3], Saša Petričević[4], Mihajlo Bošnjak[3], Nevena Zogović[5], Miloš Mandić[1], Vladimir Bumbaširević[3], Vladimir Trajković[1], Ljubica Harhaji-Trajković[5]

1Institute of Microbiology and Immunology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia;
230 West 72 St., Apartment 10A, New York, NY 10023, USA;
3Institute of Histology and Embryology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia;
4Institute of Biomedical Research, Galenika a.d., Belgrade, Serbia;
5Institute for Biological Research, University of Belgrade, Belgrade, Serbia

vericapaunovic@gmail.com; buajk@yahoo.com

During malignant transformation cells acquire changes in metabolism, signaling pathways as well as organelle content. The preferential use of aerobic glycolysis (Warburg effect), along with the increased number and volume of lysosomes can be viewed as glioma cells' Achilles heels. In the present study, we aimed to examine the *in vitro* antiglioma effects of combining lysosomal membrane permeabilization (LMP)-inducing agent N-dodecylimidazole (NDI) with glycolytic inhibitor 2-deoxy-D-glucose (2DG). NDI-triggered LMP and 2DG-mediated glycolysis block synergistically induced rapid ATP depletion, mitochondrial damage, and reactive oxygen species (ROS) production causing necrotic cell death of U251 glioma cells, but not primary astrocytes. Lysosomal cathepsin inhibitor E64 and antioxidant α-tocopherol partially prevented NDI/2DG-induced glioma cell death, thus implying the involvement of LMP and oxidative stress in the observed cytotoxicity. Likewise, LMP-inducing agent chloroquine showed synergistic cytotoxic effect with 2DG. Similarly, glucose deprivation as well as other glycolytic inhibitors, iodoacetate and sodium fluoride, synergistically cooperated with NDI, further corroborating that the observed antiglioma effect of the NDI/2DG combined treatment was indeed based on LMP and glycolysis block. Based on these results, we concluded that NDI-triggered LMP caused initial mitochondrial damage, which was further increased by 2DG causing the lack of glycolytic ATP required to maintain mitochondrial health. This created a positive feedback loop of mitochondrial dysfunction, ATP loss, and ROS production, culminating in necrosis. Therefore, the combination of glycolysis inhibitors and LMP-inducing agents seems promising antiglioma strategy.

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NANO SYMPOSIUM III

SOX3 ACTIVITY IN GLIOBLASTOMA CELLS: IS SOX3 A NOVEL MOLECULAR TARGET?

Danijela Drakulic[1], Jelena Marjanovic[1], Ander Matheu[2,3],[4],[5], Milena Stevanovic[1],[6],[7]

1Laboratory for Human Molecular Genetics, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Belgrade, Serbia;
2Cellular Oncology group, Biodonostia Health Research Institute, San Sebastian, Spain;
3IKERBASQUE, Basque Foundation for Science, Bilbao, Spain;
4CIBER de Fragilidad y Envejecimiento Saludable (CIBERfes), Madrid, Spain;
5Neuro-oncology Tumor Board, Donostia Hospital, San Sebastian, Spain;
6University of Belgrade, Faculty of Biology, Belgrade, Serbia;
7Serbian Academy of Sciences and Arts, Belgrade, Serbia

danijeladrakulic@imgge.bg.ac.rs

SOX3 plays a pivotal role in a number of developmental processes, including neurogenesis. On the other side, it was shown that SOX3 exhibits oncogenic potential in different cancer types, such as esophageal squamous cell carcinoma, ovarian cancer, T-cell lymphoma and osteosarcoma. Glioblastoma (GBM), a grade IV glioma, is the most common and lethal adult brain tumor. The median survival of glioblastoma patients is 15 months even with current therapeutic strategies which include surgical resection, radiation and chemotherapy. Literature data indicates that GBM development is governed by glioblastoma stem cells that drive tumor initiation, propagation, growth and therapy resistance.

Our results demonstrate that SOX3 is overexpressed in GBM human samples compared to nontumoral brain tissues. SOX3 overexpression is accompanied by increased proliferation, viability, migration and invasion of glioblastoma cells, as well as by enhanced activity of the Hedgehog signaling pathway and by suppressed autophagy in these cells. Furthermore, we found that SOX3 is overexpressed in patient-derived glioblastoma stem cells, as well as in oncospheres derived from glioblastoma cell lines, compared to their differentiated counterparts.

Together, these data indicate that *SOX3* expression is associated with the undifferentiated state of glioblastoma cells and that SOX3 could be considered as potential molecular target in glioblastoma.

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NANO SYMPOSIUM III

EXPRESSIONAL REGULATION OF MNSOD ACTIVITY IN γ-IRADIATED RAT BRAIN

Ana Todorović, Snežana Pejić, Ljubica Gavrilović, Ivan Pavlović, Vesna Stojiljković, Nataša Popović, and Snežana B. Pajović

Laboratory of Molecular Biology and Endocrinology, "Vinča" Institute of Nuclear Sciences, University of Belgrade, Belgrade, Serbia

anato@vin.bg.ac.rs

Radiation exposure has multiple effects on the brain, behavior, and cognitive functions. Among the brain regions, prefrontal cortex and hippocampus are the most sensitive to irradiation. Due to the physical characteristics of γ-radiation, and since the highest number of data on animals and humans were obtained using γ-rays, this type of radiation is considered a reference.

Organisms exposed to ionizing radiation are mainly damaged by free radicals, which are generated by the radiolysis of water contained in the cells. MnSOD is located in the mitochondrial matrix and serves as an effective radioprotector by clearing oxygen radicals, alleviating oxidative damage of the cell, and modulating its biological response.

In this study we examined the correlation of MnSOD expression and activity in rat hippocampus and preforontal cortex, 1 h and 24 h after cranial exposure to 2 Gy, 3 Gy, or 5 Gy of γ-rays.

Our results showed that correlation of MnSOD expression and its enzymatic activity varied depending on the tissue, the dose, and the time after irradiation. Negative correlation was more pronounced after exposure to higher doses of γ-radiation, and the effect was more prolonged in the hippocampus, pointing to higher radiosensitivity of this brain region.

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NANO SYMPOSIUM III

DO INTERMEDIATE REPEAT EXPANSION LENGTH IN C9ORF72 HAVE AN EFFECT ON CLINICS IN CASES WITH FRONTOTEMPORAL LOBAR DEGENERATION?

E.Erzurumluoglu Gokalp[1] , B.D.Ozbabalık Adapınar[2], F. Tepgec[3] , O.Cilingir[1], B. Bilgic[4], S. Kocagil[1], H. Ozen[5], B. Durak Aras[1], C. Yenilmez[6], S. Artan[1]

1Eskisehir Osmangazi University, Faculty of Medicine, Department of Medical Genetics, Eskisehir, Turkey;
2Acıbadem Hospital Neurology Clinic, Eskisehir, Turkey;
3Istanbul University, Istanbul Faculty of Medicine, Department of Medical Genetics, Istanbul, Turkey;
4Istanbul University, Istanbul Faculty of Medicine, Behavioural Neurology and Movement Disorders Unit, Department of Neurology, Istanbul, Turkey;
5 Eskisehir Osmangazi University, Faculty of Medicine, Department of Biostatistics, Eskisehir, Turkey;
6 Eskisehir Osmangazi University, Faculty of Medicine, Department of Psychiatry, Eskisehir, Turkey

ebruerzurumluoglu@gmail.com

Frontotemporal lobar degeneration (FTLD) describes a group of progressive brain disorders. One of the major genetic factors for FTLD is the expansion of a hexanucleotide (GGGGCC) in *C9orf72* gene.

In this study; it was aimed to determine the prevalence of C9orf72 repeats in 170 Turkish FTLD cases without mutation in MAPT,PGRN,CHMP2B,VCP,TARDBP,FUS genes and 100 controls by using repeat-primed (RP-PCR), and to determine the effects on the phenotype.

The pathogenic (>30) and intermediate repeats (20-29) were detected 1.2%, 3,5% in cases, respectively. The dominancy of intermediate/pathogenic repeats was seen in the cases with psychotic symptoms. The difference in allele length between the cases and controls was statistically significant ($p<0.01$). To determine whether the intermediate and ≥30-repeat allele carriers shared the *C9orf72* risk-haplotype, we examined rs4879515/rs3849942 in 100 samples and family members of patients with possibly pathogenic alleles. We identified at least one risk allele for each single nucleotide polymorphism in all intermediate and possibly pathogenic repeat carriers. We observed that ≥8 unit repeats were strongly correlated with the tagging risk alleles for both SNPs ($p<0.001$).

To our knowledge, this is the first study to evaluate *C9orf72* G_4C_2 repeats in Turkish FTLD patients. The present findings suggest that pathogenic expansions of the C9orf72 repeat are uncommon in Turkish FTLD patients. We believe that the intermediate repeat should be considered as an increased risk factor for FTLD or might play role as a modifying factor, and that the intermediate repeats should be taken into consideration especially for cases observed to have psychotic symptoms.

This study was supported by The Scientific and Technological Research Council of Turkey (TUBITAK1001-114S346)

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Friday, July 11, 2019

18:10-19:10

Room Atlantic 1

NANO SYMPOSIUM III

INSULIN SIGNALING IN THE HYPOTHALAMUS OF 5XFAD MICE AS AN ANIMAL MODEL OF ALZHEIMER'S DISEASE

Iva Lakic[1], Tanja Jevdjovic[1], Milka Perovic[2], Tamara Dakic[1], Predrag Vujovic[1], Selma Kanazir[2] and Jelena Djordjevic[1]

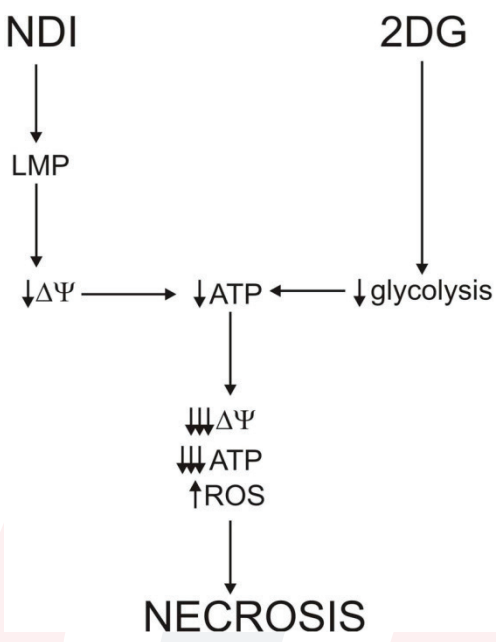
1 Department for Comparative Physiology and Ecophysiology, Institute for Physiology and Biochemistry, Faculty of Biology, University of Belgrade;
2 Department of Neurobiology, Institute for Biological Research "Sinisa Stankovic", University of Belgrade

djiva@bio.bg.ac.rs

Alzheimer's disease (AD) is a neurodegenerative disorder associated with progressive loss of cognitive function. In AD patients glucose metabolism and insulin signaling could be altered. Eight and 36 weeks old 5xFAD male mice were used as an AD model. The aim of this study was to investigate hypothalamic insulin signaling and glucose metabolism in the 5xFAD mice by analyzing insulin protein expression, insulin signal pathway and glucose transporter levels. Western blot was used to assess protein content.

Our study has shown that both insulin and insulin receptor were decreased in 36-week-old mice as compared to 8-week-old. IRS1/pIRS1, pAKT, ERK1,2/pERK1,2 contents also decreased, whereas there were no changes in pIRS2, p85 and mTOR/pmTOR levels. Astrocytic 45 kDa GLUT1 isoform, and endothelial 55 kDa GLUT1, GLUT2 and GLUT3 levels were elevated, while GLUT4 was decreased.

A better understanding of the relationship between alterations in central glucose metabolism, insulin signaling and cognitive function might provide a basis for the development of better treatment options for patients with AD.



HC01

RISING PHOENIX: DR. AYSIMA ALTINOK

Merve Sevgi Ince[1], Rabet Gozil[1] , Meltem Bahcelioglu[2], Kerem Atalar[3], Ece Alim[2], Deniz Esma Barc[1]

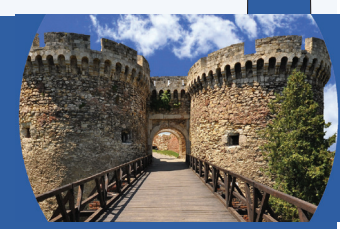
1Yüksek İhtisas University, School of Medicine, Department of Anatomy, Ankara, Turkey;
2Gazi University, School of Medicine, Department of Anatomy, Besevler, Ankara, Turkey;
3Bülent Ecevit University, School of Medicine, Department of Anatomy, Zonguldak, Turkey

msevgii94@gmail.com

For many years women have been playing an active role in many fields of medicine, yet they are rarely specialized in neurosurgery. When medical literature is reviewed, it is seen that the number of women taking up the surgical specialties is very low. In spite of this, Aysima Altınok became the first Turkish female neurosurgeon.

Dr. Altınok was born in Erzincan in 1929. There was a major earthquake in Erzincan in 1939 which was a turning point for Dr. Altınok and her family. The Altınok family, who had lost everything, experienced material and moral breakdown. After this tragic event, Altınok family moved to Istanbul. Altınok whose home was burnt to ashes in Erzincan, reborn from ashes like a phoenix in Istanbul. She was fortunate to be in the city of Istanbul where she could both get the medical education she had dreamed of and develop herself culturally. She enrolled in Istanbul University, Faculty of Medicine. In the anatomy and physiology lectures of the phase II, she noticed that nothing was completely known about the functioning of the brain. As a result of her interest in this mystery, she decided to become a neurosurgeon in the phase II. While Dr. Altınok was in phase IV, Dr. Feyyaz Berkay completed his neurosurgery training in the United States and returned to Istanbul University and he noticed her interest in neurosurgery. Upon the request of Dr. Berkay, they trend to found a department of neurosurgery for almost three years. After the failure of this initiative, she started working as a neurosurgeon assistant at Haydarpaşa Numune Hospital in 1956. At that time, Haydarpasa Numune was the only hospital providing neurosurgical education in Turkey. In 1959, she completed her residency training in neurosurgery at Haydarpasa, preparing a thesis on brain tumors and she achieved her certification as a neurosurgeon. In this manner, Dr. Altınok went down in history as the first female brain surgeon in Turkey. Finally she was appointed to Bakırköy Emrazi and Akliye Hospital and she retired after 33 years of professional life.

Thus, the entry of women into neurosurgery in Turkey was earlier than most of the other countries. Dr. Altınok was a pioneer for women dreaming of becoming a brain surgeon in Turkey. Like the phoenix's association with immortality, Dr. Altınok's contribution to the literature will be a guide for female neurosurgeons all along.



HC02

M. GAZI YASARGIL: MAN OF THE CENTURY (1950-1999)

Sami Ağuş, **Özge** *Başer,* **İskalen** *Cansu Topçu, Cihan Civan Civaş, Bayram Yılmaz*
Yeditepe ***Üniversitesi****, Tıp Fakültesi, Fizyoloji Anabilim Dalı,* ***İstanbul****, Turkey*

sami.agus@yeditepe.edu.tr

Prof. Mahmut Gazi Yasargil was born in Lice, Diyarbakır, Turkey in1925. He studied primary and high school in Ankara from 1931 to 1943. He went to Germany for university education and he started to medicine education in Friedrich Schiller University of Jena. Because of the World War II, he moved to Sweden and continued his education in University of Basel. After the graduation from University of Basel, he worked in psychiatry, internal Medicine and General Surgery as a residency. Next, he started to work with Prof. H. Krayenbühl in Department of Neurosurgery at University of Zurich in 1953 and he worked on cerebral angiography. In 1953, he discovered Orbital Venography and superior sagittal sinus thrombosis. He shot three dimensions photos of brain and he modelled venous and arterial vessels of brain. In 1957, he published first book about vertebral and basilar arteries. In addition, in 1957, he went to USA to learn stereotaxic surgery from Prof. Mundiger and Prof. Hassler. In 1958, he published a book about aneurysm and arteriovenous malformation with Prof. H. Krayenbühl. Also, in 1965 he published "Cerebral Angiography with Prof. H. Krayenbühl and then, he went to USA to learn microsurgery. He done some surgery on animals to learn microsurgery and after the turn back Sweden, he done first brain by-pass surgery in 1967. This by-pass surgery is a milestone in micro neurosurgery. In 1968, he organized micro neurosurgery courses in Zurich and 186 neurosurgeon participated this courses from different countries. In 1971 he invented his own microscopy which is still widely used in micro brain surgery. Leyla retractor, Yasargil aneurysm clips, scissors, aspirator and forceps were made with his own design, which was brand new in terms of changing the philosophy of the techniques and equipment. In 1974, modern surgery was used for the first time by him for the tumors originated from ear nerve. In 1976, skull base meningioma was operated successfully in the sense of again modern surgery. In 1984, he made a breakthrough in epilepsy surgery with not excluding a whole lobe. From 1984 to 1996 he wrote his most popular book series Microneurosurgery. In 1993, he retired in Zurich. In the following 20 years he worked actively in USA in Little Rock-Arkansas. Laboratory and Education Center established in the name of Prof. Yaşargil and his wife. He came back to Turkey in 2013 to Yeditepe University.

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Friday, July 11, 2019

13:10-15:00

Room Baltic

History Posters

HC03

THE HISTORY OF NEUROSCIENCE IN ANATOLIA AND TURKEY

Ece Alim[1], Merve Sevgi Ince[2], Deniz Esma Barc[2], Kerem Atalar[3], Rabet Gozil[2], Meltem Bahcelioglu[1]

1Gazi University, School of Medicine Department of Anatomy, Besevler, Ankara, Turkey;
2Yüksek İhtisas University, School of Medicine Department of Anatomy, Ankara, Turkey;
3Bülent Ecevit University, School of Medicine Department of Anatomy, Zonguldak, Turkey

ece.alim06@gmail.com

Neuroscience, the topmost field where specialization and subspecialization increase continuously.

Anatolia, known as Asia-Minor, is one of the most important geo-political areas of the world, from which many civilizations emerged. The first sign of neurosurgical intervention in Anatolia discovered so far is the cranium from the Neolithic Age with a large craniectomy in the left posterior frontal region. It seems a sharp chisel-like object was used to produce the hole. During the era of Hittites (1660-1190 B.C.), depression, aphasia, blindness, and deafness were explained and terms in Hittites. Asclepiades of Bithynia (124-70 B.C.) was born in today's Bursa of Turkey. He is famous for his way of treating mental disorders by restoring the harmony through occupational therapy, music, exercise. Aretaeus of Cappadocia tried to find an anatomical explanation on the curious phenomenon of lateralization. He was the first to describe the aura and hallucinations preceding epilepsy, observing that bad-smell, and noises in the ears, tremors and weird sensations in the hands or feet may occur before the seizure. Rufus of Ephesus (110-180 B.C.) distinguished the nerves of motion from the nerves of sensation. He defined the course of the optic nerves in detail and described the parts of the eye. The most important physician of the Greco-Roman period was Galen of Pergamum. One of Galen's important contributions was the classification of the cranial nerves. In the Byzantine Period, some important contributions were made to neuroscience. Oribasius of Constantinople (325-403 B.C-today's İstanbul) gave precise descriptions of the result of cuts at different levels of the spinal cord.

Şerafettin Sabuncuoğlu (1385-1470 Ottoman Empire) is one of the most famous surgeons in Anatolia. He is the writer of the first medical textbook with colorful illustrations. Sabuncuoğlu explained migraine headaches, epilepsy, hematomas and fluid collections in the head and treatment of these. Despite the opposing Islamic instructors, Bedbaht Emir Çelebi supported the anatomical dissections on the human body, which he declared crucial in understanding and treating the illnesses.

After the foundation of the Republic of Turkey (1923), Hulusi Behçet was a Turkish scientist born in Istanbul. He discovered a new disease, which was named after him in 1937 as "Behçet's Disease". Doubtlessly the most important figure in the history and present of Turkish Neuroscience is "The man of the Century", M. Gazi Yaşargil. He's the pioneer of microneurosurgery. Throughout the history of Turkey, in the field of neuroscience many valuable world-renowned scientists have grown.

HC04

THE RISE OF CELLULAR ELECTROPHYSIOLOGY IN THE BALCANS

Nedeljkov V [1] & Andjus P [2]

1 Institute for Pathological Physiology, School of Medicine University of Belgrade, Belgrade, Serbia;
2 Institute for physiology and biochemistry "Ivan Djaja", Faculty of Biology University of Belgrade, Belgrade, Serbia

pandjus@bio.bg.ac.rs

The revolution of electrophysiology started with Alan Hodgkin's and Andrew Huxley's first intracellular recording of action potential in 1939. From there on this wave spread all over the world and had a particular influence also in Belgrade, Yugoslavia. Pioneers of one of the first schools of modern electrophysiolgy in the Balcans were Profs Bogdan Beleslin, School of Medicine and Mira Pašić, School of Natural Sciences, University of Belgrade. Both learnt their craft abroad and transferred the knowledge back home (opposite to today's "brain drain" trend).

After his study visit at Grundfest's lab at Columbia University Beleslin returned to Belgrade to build one of the first electrophysiology labs in the region. He was helped by George Katz renowned electroengineer from Columbia.

The first paper in the field of cellular electrophysiology Beleslin and coworkers have published on the lobster axon in Nature (1965), that was also a pioneering study on neuroimmunology. Later Beleslin has established as his main experimental model the Retzius nerve cell of the leech.

Mira (Senberger) Pašić started her research carrier in the group of prof. Jean Giaja who was the founder of the Belgrade School of Physiology. She also specialized abroad - in Cambridge and London where she learnt the electrophysiology of the nervous system in the labs of profs B.C. Mathews and G.L. Brown. Her first co-authored paper on the electrophysiology was on the rat sympatic cervical ganglion (1967). On the same year she also published a study on the motoneurons of the cat. Later in 1968 and 1969 she returned to the fascinating field of hibernation and published comparative works on the cervical ganglion of the non-hibernator (lab rat) and a hibernator (ground squirrel, Citellus citellus). Later on she developed the model of neurons in the ganglia of the snail, Helix pomatia that was studied for many years and also after her demise, in her still existing lab "Number 13" in the Institute for Biology Research in Belgrade.

The works of Beleslin and Pašić were the foundation of a particular School of electrophysiology in Belgrade, surely one of the first on the Balkans, that has developed in many directions, egs. from intracellular neuronal recordings to the in vivo chronic brain electrophysiology, or from patch clamp recordings to plant electrophysiology.

HC05

WHO IS ŞEREFEDDIN SABUNCUOĞLU?

Atalar K [1], Barc DE [2], İnce MS [2], Alim E [3], Bahçelioğlu M [3], Gözil R [2]

1 Zonguldak Bülent Ecevit University, School of Medicine, Department of Anatomy, Zonguldak, Turkey;
2 Yüksek İhtisas University, School of Medicine, Department of Anatomy, Ankara, Turkey;
3 Gazi University, School of Medicine, Department of Anatomy, Ankara, Turkey

krmtlr@gmail.com

When considering the history of surgery along with medicine, one can argue that they started, evolved and changed in a similar way and at a similar rate the human civilisation did. In the ancient world, the Romans as well as the Greeks were ahead of the game in medicine thanks to names like Hippocrates and Galen who lead the way.

It wasn't until the 1400s that medical books in Turkish were written in Anatolia which constitute the main sources of reference to those interested in the history of medicine in the region. A prime example to the books of this time is ''Cerrahiyetü'l-Haniyye" by Şerefeddin Sabuncuoğlu, a Turkish physician of the time.

Born in 1385, Sabuncuoğlu started his medical training in the hospital of Amasya (also a medical school) at the age of 17. After 14 years of service in this institution he worked in various other Anatolian cities like Kastamonu, Gerede and Bolu. At the age of 83, he published his most influential work, Cerrahiyetü'l-Haniyye, which deals with fields including orthopedics and traumatology, thoracic surgery, dental medicine, urology, plastic surgery, anorectal surgery, general surgery, pediatric surgery, and neurosurgery. In the field of neurosurgery the book mentions various ways of threating spinal dislocations, sciatica and back pain.

Sabuncuoğlu was special in a lot of ways. He was a good clinician, writer, illustrator and a good teacher.

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HC06

THE FIRST TREPANATION TECHNIQUE IN TURKEY AND DR. CEMIL TOPUZLU

Esma Deniz Barc[1], Meltem Bahcelioglu[2], Rabet Gözil[1], Ece Alim[2], Kerem Atalar[3],Merve Sevgi Ince[1]

1Yuksek Ihtisas University, School of Medicine, Department of Anatomy, Ankara ,Turkey;
2Gazi University, School of Medicine, Department of Anatomy, Ankara, Turkey;
3Zonguldak Bulent Ecevit University, School of Medicine, Department of Anatomy, Zonguldak, Turkey

dnzbrc7@gmail.com

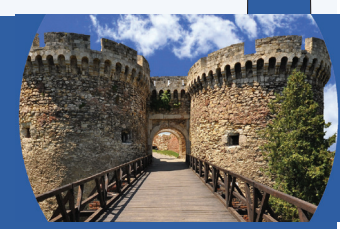
Trepanation is the operation performed on the skull of a living person or a dead person, adhering to a specific technique for a projected purpose. Trepanation history dates back to prehistoric times. However, ritual, magical and therapeutic aspects of the human brain is the oldest type of brain surgeries. Due to its historical background, the disciplines of archeology and anthropology were also closely related to this method. Conducting this procedure on a live human needs deep knowledge and expertise in this field.

This operation used by wizards and physicians in Africa and Oceania, priests in the Hawaiian island. In Kenya, trepanation in the Kisii tribe became a popular carreer from one generation to another. In Algeria, magician-surgeons used to teach this technique in schools.

Cemil Topuzlu was the first person who used the trepanation in Turkey. He completed his medical education in 1886. After working in a hospital for a year, he was sent to France to acquire higher skills in the surgery. After three years working in France, he returned to Turkey in 1890 and started practicing in surgery. Dr. Topuzlu has sets an example to his colleagues by focusing on the importance of anatomy knowledge. He has also made important contributions to Turkish medicine on the subject of septicemia, asepsis, and antisepsis.

Cemil Topuzlu (1866-1958) collected his observations in his book Mémoires et Observation Médicales, published in 1905 in French. Trepanation is presented in chepter 8 of this book. In the conclusion part of his description he says: “The knowledge based on the localization of motor centers in human, has great importance for treatment. Thanks to the localization information is based on knowledge of the trepanation the first surgery was performed in Turkey in February 24, 1892”. This case was presented by Cemil Topuzlu at the International Medical Congress in 1894 in Lyon.

As a result, the technique of trepanation had used primarily in Turkey by Dr. Topuzlu and then was started to use all neuroscience world.



HC07

CONNECTING THE PAST AND THE PRESENT: HISTORICAL BACKGROUND OF NEUROSCIENCE DEVELOPMENT IN ANATOLIA

Ali Tuğberk Bulut[1],Emel Ulupinar[2,3]

1 Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey;
2Anatomy Department, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey;
3Interdisciplinary Neuroscience Department, Health Institute, Eskisehir Osmangazi University, Eskisehir, Turkey

alitugberkbulut@gmail.com

Historical development of neurological sciences in Anatolia can be grouped into Antic ages and the period after Turks had immigrated to the Anatolia. First physicians had emerged during Hittite civilization and some neurological terms such as depression, aphasia, blindness, and deafness were first used by them. Opium Poppy also traces its origins to a Hittite tribe and the seeds yielding gum opium-heroin is derived from it- is sold for pharmaceutical concerns and morphine was used to ease tooth pains and other maladies. A skull of a person who underwent craniotomy in this period and survival of the individuals after trepanation suggest that advanced surgical techniques similar to today's approaches were used in the Urartu Age. Galen of Pergamum named many structures of the nervous system, which are mostly still in use, and classified cranial nerves. The medical doctrines in the classic treatises of the Greco-Romans and the Syrians were translated to Arabic, then translated again into Latin. This helped to prevent loss of the classics in the Dark Ages. Orbasius of Constantinople classified spinal cord injury levels, the effects of excessive CSF. Alexander of Tralles gave accurate information on headaches, mental disorders, epilepsy and their origins.

Both Anatolian Seljuks and Ottomans used Islamic medical doctrines derived basically from Greco-Roman and Islamic scientists. The first organized hospitals in the world was built during this period. Its psychiatry department was one of the contemporary and frontier centers. Ottoman medicine was influenced by Western medicine in the 15th century, but remained at the limits of Muslim medicine until the 19th century. Following failure of traditional treatments, ''Royal College of Medicine" was founded in 1939. Mazhar Osman (1884-1955), neuropsychiatrist completed his training in Germany with Kreaplin (the founder of organic psychiatry),published the first Turkish neuroscience journal.

After foundation of Turkey by Mustafa Kemal ATATURK in 1923, many scientists were sent abroad for training. When they returned, scientific studies in neuroscience have started to contribute to the literature in Istanbul (1950s), Ankara (1965) and Ege (1967) Universities.

Professor Muhittin ERER built first experimental animal breeding facility and ''Experimental Research Institute" on 12.01.1945. The "Institute of Neurological Sciences and Psychiatry" was established in 1982 at Hacettepe University, to promote integrative research in basic and clinical neurosciences.

Finally "Neuroscience Society of Turkey (TÜBAS)" was founded by Professor Nuran HARİRİ in 1991. Now, there are more than 15 neuroscience departments in Turkish Universities offering Msc and PhD degrees.

HC08

NEUROLOGIST, BUT NOT ONLY THAT...

Bulat P [1], Knežević B [2], Petronijević M [1]

1 Student Section of Serbian Neuroscience Society, Belgrade, Serbia;
2 University of Belgrade School of Medicine, Belgrade, Serbia

bulat.petar@yahoo.com

Lazar K. Lazarevic was born in Šabac, a town in western Serbia. He lived for only 39 years (1851–1891). Despite his short life and short professional career, he left behind a large body of work. He wrote nine beautiful tales, thirteen fragments and one hundred and ten letters to the members of his family. But, in the 1877-1890 period also he wrote seventy eight scientific medical papers. He was an exceptional physician and scientist, but also a talented writer and translator, called the Serbian "Turgenev". Lazarevic's short stories represent masterpieces of Serbian literature. He came very slowly to his full stature as a short story writer reading Turgenev, Gogol and other great writers. That helped Lazarević to formulate his own aims as sa short story writer. His two most famous stories are: "To Matins with my father for the First time" and "The People Will Reward All This". He studied law faculty of Belgrade's Grandes écoles (Belgrade Higher School), but in 1871, decided that medicine was his true calling.

Medical career:

Dr. Lazarevic studied medicine at the Friedrich-Wilhelm University of Berlin and completed his doctoral thesis on the effects of mercury on experimental animals in 1879.

In 1881, he was appointed as the Head of the Internal Medicine Department of the General State Hospital in Belgrade, as well as a member of the General Medical Council of the Kingdom of Serbia. In 1888, he was elected a Corresponding Member of The Serbian Royal Academy, and in 1889 he became the doctor of the Royal Court of the King of Serbia, Milan Obrenovic. Dr. Lazarevic was a highly moral and noble personality, loyal to his profession and to his people until the last moment of his life. He died of tuberculosis in 1891. Lazarević sign:

The greatest contribution of L. Lazarević to medical science is his description of the straight leg raising test, used to diagnose lumbar root compression. An analysis of the historical events shows that he was actually the first to publish the description of this test, and to identify the stretching of the sciatic nerve as the cause of the pain. Although he was the first to describe this sign, he never claimed priority. All the medical students and practicing neurologists throughout the world remember Charles Lasègue (1816-1883) for straight-leg raising test, although Lasègue never published a description of this sign.

HC09

ASCLEPIUS: THE MAN AND THE MYTH

Fertan E, Brown RE

Dalhousie University, Department of Psychology and Neuroscience, Halifax, Nova Scotia, Canada

emre.fertan@dal.ca

Known as Asclepius, Asklepios, Aesculapius or Hepius in various cultures and stories, Asclepius is one of the most colourful figures of antique medicine. Often shown with his famous rod, the most famous physician of his time was even considered a god. He often appears in classic Greek myths and even today it is possible to visit the Asklepions, which were the ancient healing centres or hospitals located in modern day Greece and Turkey. In this poster, we gathered some of the most famous stories about the God of medicine regarding his birth, education, family, death, and legacy.

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History Posters

HC10

ORBELI'S PHENOMENON

Ghulikyan L.A., Ghukasyan G. V., Ayvazyan N. M.

L. A. Orbeli Institute of Physiology, Yerevan, Armenia

lusine.ghulikyan@gmail.com

Leon (Levon) Orbeli was an outstanding physiologist, scientist, methodologist, scientific successor of I.P.Pavlov. He was also a founder of huge scientific school. Orbeli and his school have developed new directions in physiology.

He not only kept the physiology as a science in the time of the 1st and 2nd World Wars, the Great Patriotic War, but also made an incredible contribution to its development as a fundamental science. His achievements have been a turning point in physiology as a science all over the world.

Orbeli was the first in the USSR to organize the Laboratory of Developmental Physiology. The laboratory studied age-related changes of metabolism in animals and children. His research concerning the impact on the human body of high and low barometric pressure found practical applications in military medicine and in the organization of the conditions of military service. Orbeli's investigation of physiological processes in high stratosphere is accepted as base of space physiology in USSR.

Using discoveries in basic science, teams of scientists, led by Academician Orbeli could develop applied research.

In addition to the data presented about Levon Orbeli, as a brilliant scientist, we have the history of his life, told by his relatives and friends. Also, there is more detailed information about his research activities. It's possible to describe the achievements of Leon Orbeli endlessly. So we would like to have an opportunity to represent the whole genius of the outstanding physiologist. We can also describe all his awards and the accompanying stories of those events.

HC11

HEROPHILOS - THE GREAT ANATOMIST AND NEUROSCIENTIST OF ANTIQUITY

Buse Kayhan[1], Pelin İlhan[1], Şeyhmus Bayar[1], Esra Candar[1], Gülgün Şengül[1,2]

1Department of Neuroscience, Institute of Health Sciences, Ege University, Izmir, Turkey;
2Department of Anatomy, Faculty of Medicine, Ege University, Izmir, Turkey

kayhanbuse@gmail.com

Herophilos was born around 335 B.C in Chalcedon known as Kadikoy in Istanbul, Turkey. He was known as 'The Father of Anatomy'. He examined the body of animals and human comparatively. He disssected the human body and seperated brain from cerebellum. He described the brain as the seat of the intelligence. He distinguished the nerves according to their functions: 'movement (motor)' and 'sensory', and described at least six cranial nerves and the lower brainstem and spinal cord. He also identified and described several brain structures. Some of the anatomical terms which he used are still used, such as the internal surface of the occipital bone known as the Herophilos' press (torcular Herophili). His work on neuroanatomy in his age is astounding.

HC12

DOCTORS WITHOUT BORDERS:THE JOURNEYS THAT SHAPED MODERN DAY NEUROSCIENCE IN SERBIA, ROMANIA AND TURKEY

Mishra A.

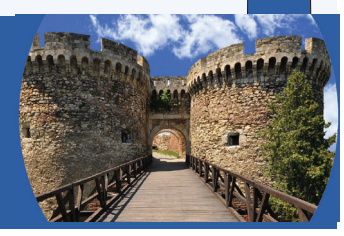
National Center for Biological Sciences, Bangalore, India

aditi.niser@gmail.com

Science, has always existed beyond narrow political boundaries. Neuroscience in particular has seen an admixing of people from different walks of life. Different nationalities, different ethnicities and temperaments come together in the retelling of its story.

As we trace the history of neuroscience in Serbia, Romania and Turkey one cannot help but notice the lengths the pioneer neuroscientists undertook to learn, develop and refine their craft. Their triumphs and struggles especially due to war, are a mirror not only to the nations of their origin but to the entire Europe of their times.

This poster honours the struggles and triumphs of Dr. Laza K. Lazarević, Dr. Sofia Ionescu-Ogrezeanu and Dr. Hami Dilek. Their lives are testaments to how history and circumstances shape science and the lives that depend on it.



HC13

THE ORIGIN OF NEUROSCIENCE AT THE INSTITUTE OF MEDICAL AND CLINICAL BIOCHEMISTRY, SCHOOL OF MEDICINE, UNIVERSITY OF BELGRADE

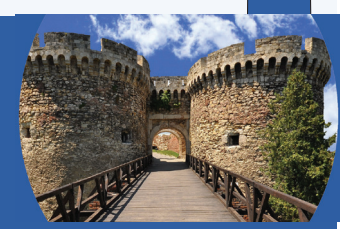
Sonja Misirlic-Dencic, Zeljka Stanojevic, Tatjana Nikolic, Andjelka M. Isakovic, Milica Velimirovic-Bogosavljevic, Aleksandra Isakovic, Ivanka Markovic, Natasa Petronijevic, Ljubisa Rakic

Institute of Medical and Clinical Biochemistry, School of Medicine, University of Belgrade, Belgrade, Serbia

sonja.misirlic-dencic@med.bg.ac.rs

The development of neuroscience at the Institute of Medical and Clinical Biochemistry has begun long before the Institute's foundation at 1964, when it separated from Institute of Physiology. The principal investigator of the first scientific project related to neuroscience at our Institute, "Biochemistry of central nervous system", was Prof. Ljubisa Rakic. He was also the founder of the Laboratory of Neurophysiology and Neurochemistry at the Institute for Biological Research "Sinisa Stankovic" and International laboratory for brain research in Kotor, Montenegro, under the auspices of UNESCO and National Institute of Health. During the seventies, Prof. Rakic's collaborators, Prof. Bogomir Mrsulja and Prof. Dejan Micic were visiting scientists at National Institute of Health in Bethesda (USA) and concentrated on the research of biochemical characteristics of brain capillaries. In the eighties Prof. Mrsulja founded Laboratory for pathological neurochemistry, whose research focused on ischemic brain insult and role of neurotransmitters in this processes. Pioneering work of Prof. Mrsulja and his original hypothesis on mechanisms of the occurrence of ischemic cerebral edema and possible therapeutic approach was recognized as revolutionary worldwide. Furthermore, his drive to connect basic and clinical research motivated one of his PhD students, Prof. Vladimir Kostic to continue his scientific work as neurologist. In the nineties, one of the scopes of neuroinvestigation at the Institute was transport of different endogenous hydrophilic molecules and their analogues through the barriers of the brain. At that time, the model of in situ perfusion of guinea pig brain and sheep choroid plexus were established by Prof. Berislav Zlokovic, Prof. Bogdan Djuricic and Prof. Zoran Redzic. Their work throughout more than two decades contributed to better understanding of the biochemical and physiological roles of brain barriers, and possibilities for therapeutic modulation. At the beginning of new millennium the scope of investigation has changed towards in vitro models of neuronal and glial cells' primary cultures and exploration of molecular basis of neurodegenaration and neuroinflammation, together with research of synaptic plasticity in psychiatric disorders particularly in schizophrenia, depression and chemical and vascular brain injury. The Institute continues the tradition and organizes education of future PhDs in Neuroscience module and has ongoing project in this field.

Highly cited publications, numerous long-lasting and important collaborations with prominent neuroscience centers, outstanding scientists who have made significant impact to the field both in Serbia and abroad including five academicians, make an impressive legacy and encouragement for future generations.



HC14

MEMORY LANE TREE OF BRAIN BARRIERS RESEARCH AT THE INSTITUTE OF MEDICAL AND CLINICAL BIOCHEMISTRY, SCHOOL OF MEDICINE, UNIVERSITY OF BELGRADE

Sonja Misirlic-Dencic [1], Aleksandra Isakovic [1], Ivanka Markovic [1], Zoran Redzic [2], Ljubisa Rakic [1]

1 Institute of Medical and Clinical Biochemistry, School of Medicine, University of Belgrade, Belgrade, Serbia;
2 Department of Physiology, Faculty of Medicine, Kuwait University, Kuwait, Kuwait

sonja.misirlic-dencic@med.bg.ac.rs

As soon as the modern concept of the blood-brain barrier was established by Hugh Davson, a leading researcher at King's College London (KCL), his research team was enlarged. Namely, Berislav Zlokovic, Dusan Mitrovic, and Bogdan Djuricic, researchers from School of Medicine, University of Belgrade

(SMUB) joined Davson's group at KCL and established a model of in situ perfusion of guinea pig brain to explore blood to brain solutes' transport. The model was immediately implemented at Institute of Biochemistry (IB-SMUB), and used to define transport systems for the uptake of amino acids and nucleic acids precursors and their analogues. This work was done by Zoran Redzic and Ivanka Markovic, under the supervision of Ljubisa Rakic. At that time Malcolm Segal, Milo Lipovac, Jane Preston, Jasmina Mackic joined the KCL team and important collaboration continued. Approximately 20 research papers and several MSc/PhD theses were derived from this research in the period 1986-1996.

n the mid nineties Malcolm Segal introduced a technique of in situ perfusion of sheep choroid plexus (CP) at IB-SMUB, and the focus of investigation moved in the direction of blood-CSF barrier as a possible target for therapeutical approach. At that time the KCL team was enlarged by Sarah Thomas, while Ivanka Markovic and later Jovana Gasic joined the Belgrade team. Obtained results showed, inter alia, that nucleic acid precursors are transported by saturable systems without significant metabolic transformation in CP. This research resulted in 12 research papers that were published between 1996-2006.

In 1998-2000, in vivo techniques, brain uptake index and brain efflux index were introduced at IB-SMUB and used to elucidate the net transport of solutes between the blood and brain extracellular fluids. This work was mainly conducted by Aleksandra Isakovic, who joined the team.

At the beginning of new millennium Zoran Redzic moved to Malcolm Segal's lab at KCL and established primary cell culture of brain barriers. His research was improved by Aleksandra Isakovic and Sonja Misirlic-Dencic who then introduced primary cell culture of sheep CP at IB-SMUB. This model directed further research towards cellular and molecular level and was used for functional characterization of CP's nucleoside transporters.

The results from brain barriers transport research at IB-SMUB, fruitful cooperation with KCL that lasted for more than two decades and involved more than twenty researchers from both sides, were incorporated in numerous thesis, highly cited publications and respected textbooks and present valuable legacy and inspiration for future achievement.

HC15

DIMITRIE CĂLUGĂREANU – A MAN BEYOND HIS EPOCH: FROM FLYING IN A BALLOON TO NEUROPHYSIOLOGY

Beatrice Mihaela Radu

Department of Anatomy, Animal Physiology and Biophysics, Faculty of Biology, University of Bucharest, Bucharest, Romania

beatrice.radu@bio.unibuc.ro

Dimitrie Călugăreanu (1868-1937) was a Romanian physician and physiologist. He got his bachelor degree in Natural Sciences (1894) at the Faculty of Science, University of Iași and his bachelor degree in Medicine (1897) at the Faculty of Medicine in Iași, Romania.

Călugăreanu was appointed Research assistant in the Laboratory of Morphology at the University of Iași, Romania (1894-1897), under the supervision of Prof. Cantacuzino. The Romanian Academy awarded him a one-year study fellowship at the Institute of Physiology in Berlin (1898). He got his bachelor degree in Natural Sciences at the University of Sorbonne, Paris (1900). Călugăreanu did his first researches in hematology flying in a balloon (1901) being supported by a grant from the Commune of Paris. He defended his PhD in Sciences (1902) at the University of Paris, under the supervision of the famous French physiologist Albert Dastre, that in turn was Claude Bernard's student. Although, Prof. Dastre recommended him for a position at the University of Geneva, he declined this offer and returned to Romania.

He was employed Professor at the Superior School of Veterinary Medicine, Bucharest (1902-1905) and Associate Professor of Physiological Chemistry at the Faculty of Science, University of Bucharest (1908-1919), being a pioneer of Romanian biochemistry. Following the Great Union of Transylvania with Romania (1918) and the foundation of the University of Cluj, he was appointed Professor of General Physiology at the Faculty of Science (1919-1926). At the same university, he was nominated Dean of the Faculty of Science (1919-1921) and Rector (1921-1922). In 1920, he was elected Corresponding member of the Romanian Academy. He was awarded with: "Order of the Crown" (1920),

"Officer of the Public Instruction of the French Republic" (1920), "Legion of Honour" (1924). He was invited to became Director of the Institute of Physiology, University of Bucharest (1926), where he worked until its death (1937). In time, the Institute of Physiology became the Department of Anatomy, Animal Physiology and Biophysics.

Călugăreanu studied the effects of nerve compression using an original device and demonstrated alterations in nerve conduction and changes in the myelin/axon ratio. He also performed surgical crossed sutures of motor-to-sensory and secretory-to-inhibitory cranial nerves demonstrating the absence of "nerve specific energy" (theory of Johannes Müller). Beside neurophysiology, his research focused on hematology, mineral bone metabolism and respiration, and he published numerous books, studies and articles in prestigious journals.

HC16

ALEXANDRU M. VITZU – FOUNDER OF THE ROMANIAN SCHOOL OF EXPERIMENTAL PHYSIOLOGY

Beatrice Mihaela Radu, Maria-Luisa Flonta

Department of Anatomy, Animal Physiology and Biophysics, Faculty of Biology, University of Bucharest, Bucharest, Romania

beatrice.radu@bio.unibuc.ro

ALEXANDRU M. VITZU [VITZOU] (21 November 1853, Săvineşti, Neamţ county - 25 December 1902, Bucharest) was a Romanian zoologist. He got his bachelor degree in Natural Sciences at the Faculty of Science in Iaşi, Romania. Vitzu followed his doctoral studies at the University of Sorbonne, Paris, France between 1877 – 1882 under the supervision of Prof. Paul Bert and he defended his PhD thesis in 1882 on the topic "Researches on the structure and formation of teguments in Decapod Crustacea". Once returned in Romania, Vitzu became a Professor at the Department of Zoology and Animal Physiology of the Faculty of Science at the University of Bucharest. In the period 1885-1888, he was General Inspector of the Schools. He was the founder of the Romanian school of experimental physiology and he was a pioneer of endocrinology in Romania. He performed various studies on the internal renal secretion on the secretion of internal glands or on the cardiac action of digitalin. He was a pioneer in neurophysiology. Vitzu discovered that, after the resection of the occipital lobes, in which the visual hubs are located, animals could recover a certain capacity of visual orientation after a while. He attributed this fact to nervous regeneration. Now we know that the phenomenon of blindsight is actually generated by the fact that some secondary connexions between the optic tract and the superior colliculi can be still maintained. These allow for the continuation of some residual sight in persons suffering from lesions of the occipital striate cortex. Vitzou's experiments were done on dogs or monkeys. He also has studied the excitability of grey matter from the spinal cord in birds. He transformed his own house (Enei Street) in an Institute of Physiology, and student classes / researches laboratories were organized up to 1926, when his successor Prof. I. Athanasiu could move the Institute of Physiology in the new building of the Faculty of Biology (Splaiul Independenţei 91-95), where it is presently located. He was a member of the Society of Biology and Zoology from Paris, France. On 7 April 1897, he was elected Corresponding Member of the Romanian Academy.

HC17

SINGLE-UNIT RECORDING AT THE LABORATORY OF NEUROPHYSIOLOGY IN NOVI SAD

Danijel Slavić, Nada Naumović, Oto Barak, Miodrag Drapšin, Vedrana Karan, Aleksandra Rakovac

University of Novi Sad, Faculty of Medicine, Department of Physiology, Novi Sad, Serbia

danijel.slavic@mf.uns.ac.rs

Several years after the founding of the medical faculty, in 1965 a Laboratory of Neurophysiology was established at the Department of Physiology. Its founder was Prof. Dr. Mihailo Baić who managed to master sophisticated neurophysiological methods in Moscow and succeded to implement them in his parent institution. The research basis constituted of microelectrode and stereotactic methods for registration of single neuron activity, mainly during free behaviour of laboratory animals. In 1971, a fourteen-channel EEG machine

(Galileo E 14-b) was purchased and a Pavlovian chamber was constructed. This provided new opportunities for precise registration of individual and collective neuronal activity. Although confronted with a number of financial difficulties, researchers from the Laboratory were able to follow modern standpoints in neurophysiology. It had always been given great attention to the acquisition of modern equipment. At the end of 1970s a video camera (ITC IKEGAMI model CTC-5000) was purchased for monitoring of laboratory animals during their free behaviour which provided the opportunity for further analyses of recorded material. In 1981, a modern computer system DELTA 340/10 (Iskra-Delta, Kranj) with 128 KB of internal memory was acquired. Demanding and robust in its dimensions, this computer system enabled bioelectric potentials to be analyzed in real time. By introducing microiontophoretic technique, the study of different chemical substances on single-neuron activity began. The most commonly used were neurotransmitters like acetylcholine and norepinephrine, but also cytostatics, antibiotics, chemical warfare agents, etc. Special focus was paid to the mechanisms of learning for which the sea slug, Aplysia depilans, was appropriate model. Research on this animal model was carried out at the Institute of Marine Biology in Kotor where was present close cooperation with numerous international researchers in the field of neurophysiology. Although relatively small in its dimensions, the Faculty of Medicine in Novi Sad achieved to follow contemporary viewpoints in neurophysiology and to provide new scientific insights in this interesting and non-stop growing scientific field.

HC18

THE HISTORY OF NEUROSCIENCE IN SERBIA

Dolika Vasović[1], Dušan Mladenović[2], Aleksandra Rašić Marković[3], Dragan Hrnčić[3], Olivera Stanojlović[3]

1Clinic for Eye Diseases, Clinical Centre of Serbia, Belgrade, Serbia;
2Institute of Pathophysiology "Ljubodrag Buba Mihailovic", Faculty of Medicine, University of Belgrade, Belgrade, Serbia;
3 Laboratory of Neurophysiology, Institute of Medical Physiology „Richard Burian", Faculty of Medicine, University of Belgrade, Belgrade, Serbia

dolika.vasovic@gmail.com

Neuroscience has a long tradition in Serbia since the beginning of the 20th century. Nowadays 16% of researchers in biology and medicine area, and 3-4%of total 13760 researchers in Serbia, are in neuroscience. We are going to mention the greatest neurologists and neuroscientists, who deserved with their lifetime achievement that some hospitals, institutes, and even streets bear their name.

Laza K. Lazarević graduated from the Faculty of Medicine in Berlin and received his doctor's degree in 1879. He was the founder of laboratory diagnostics in Serbian medicine and of the first modern geriatric hospital in this part of Europe. The best known contribution of Laza K. Lazarević was his description of a sign that is today called after him - the "Lazarević sign".

The founder of physiology studies in the Balkans and the pioneer of research on hypothermia, Ivan Djaja had his most notable papers in the field of thermoregulation and bioenergetics. This doctor honoris causa of Sorbonne was an associate member of the National Medical Academy in Paris for his seminal work on the behavior of deep cooled warm blooded animals.

Richard Burian founded the Institute of Physiology and Histology in Belgrade in 1927. In the first few years, within the Institute of Physiology (today – the Institute of Medical Physiology), scientific research was progressing in several departments, including Physico-Chemistry, Chemical Physiology, Microchemistry, Electrophysiology, Graphics working with the operating theatres. Richard Burian was a recipient of several medals and honors: the Order of the Romanian Crown of 3rd class (in 1931), the Order of Saint Sava of 2nd class (in 1934) and the Order of the Yugoslav Crown of 2nd class (in 1936).

Ljubodrag Buba Mihailović was one of the greatest researchers in the area of neuropathophysiology and epileptogenesis in the middle of the 20th century. He was the first scientist in Yugoslavia that registered electrical phenomena in the neurons by intracellularly placed electrodes, and that used molecular techniques in the investigation of cellular basis of learning and immunopathogenesis of expreimental allergic encephalomyelitis.

Radoslav K. Andjus was a professor of physiology and biophysics at the University of Belgrade with over 190 papers in the area of thermophysiology. He also contributed significantly to the fields of brain metabolism, electroretinography, as well as biophysical modeling and theoretical biology. On the heritage of these famous teachers, many scientists are devoted to the neuroscience with great success nowadays.

FENS Regional Meeting
Belgrade, Serbia, July 10–13, 2019
ДНС SNS Друштво за неуронауке Србије Serbian Neuroscience Society
National Neuroscience Society of Romania
Neuroscience Society of Turkey

Thursday, July 11, 2019

13:45-15:00

Room Atlantic 1
Room Atlantic 2

POSTER SESSION 1

P001

INTERPLAY BETWEEN SEROTONIN RECEPTORS AND CELL ADHESION MOLECULE L1 IN THE REGULATION OF NEURONAL MORPHOLOGY

Daria Guseva[1,2], Simon Bennet Sonnenberg[1], Sophie Kristin Schade[1], Christoph Göhr[1], Monika Bijata[3], Jakub Wlodarczyk[3], Evgeni Ponimaskin[1]

1Department of Cellular Neurophysiology, Hannover Medical School (MHH), Hannover, Germany. 2Department of Clinical Nutrition, Prevention and Gender Research, University of Hohenheim, Stuttgart, Germany. 3Department of Molecular and Cellular Neurobiology, Nenski Institute, Warsaw, Poland.

daria.guseva@uni-hohenheim.de

Aims: Stress-related disorders are known to be associated with functional disturbance of neuronal adhesion molecule L1, which is critically involved in axonal development as well as neuronal survival and outgrowth. In this study, we investigated a possible interplay between L1, serotonin receptor 5-HT4 (5-HT4R), and matrix metalloproteinase-9 (MMP-9), which are known to contribute to learning and long-term memory, and are also involved in various central and peripheral disorders, including neurodegenerative disease and depression.

Methods: Morphological and biochemical analysis of dissociated mouse hippocampal cell cultures and HEK cells; immunofluorescence analysis; zymography; Western Blot; co-immunoprecipitation.

Results: We have demonstrated that 5-HT4R, MMP-9 and L1 are tightly co-localized at the synapses of cultured hippocampal neurons. In addition, recombinant 5-HT4R and L1 can physically interact at the cell membrane of transfected HEK293 cells. Furthermore, we have found that stimulation of endogenous 5-HT4R in hippocampal neurons induces the release of enzymatically active MMP-9, which in turn can cleave neuronal L1. We have also shown that L1 fragments generated by MMP-9 cleavage can modulate the process of spine formation in cultured hippocampal neurons.

Conclusions: Our results demonstrate that (i) 5-HT4R forms a complex with adhesion molecule L1 at the plasma membrane and that (ii) serotonin might regulate the functions of L1 in a 5-HT4R/MMP-9-dependent manner. Our data thus suggests a novel molecular mechanism by which serotonin can regulate the formation and plasticity of neuronal networks via homophilic/heterophilic interaction and paracrine functions of L1.

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POSTER SESSION 1

P002

ANTIPSYCHOTIC MODULATION OF PKA- AND GSK3B-MEDIATED PATHWAYS AND THE NMDA RECEPTOR IN THE VENTRAL TEGMENTAL AREA AND SUBSTANTIA NIGRA OF RATS

Bo Pan[1,2,3], Chao Deng[1,2]

1Antipsychotic Research Laboratory, Illawarra Health and Medical Research Institute, Australia;
2School of Medicine, University of Wollongong, Wollongong, NSW, Australia;
3Department of Pharmacy, Medical College of Yangzhou University, Yangzhou, Jiangsu, China

chao@uow.edu.au

Aims: Antipsychotics exert therapeutic effects by modulating various cellular signalling pathways and several types of receptors, including PKA- and GSK3β-mediated signalling pathways, and NMDA receptors. The ventral midbrain, mainly containing the ventral tegmental area (VTA) and substantia nigra (SN), are the nuclei with dopamine origins in the brain, which are also involved in the actions of antipsychotics. Whether antipsychotics can modulate these cellular pathways in the ventral midbrain is unknown.

Method: Male rats were orally administered aripiprazole (0.75mg/kg, t.i.d. (ter in die)), bifeprunox (0.8mg/kg, t.i.d.), haloperidol (0.1mg/kg, t.i.d.) or vehicle for either 1 week or 10 weeks. The levels of PKA, p-PKA, Akt, p-Akt, GSK3β, p-GSK3β, Dvl-3, β-catenin, and NMDA receptor subunits in the VTA and SN were assessed by Western Blots.

Results: The results showed that chronic treatment of aripiprazole selectively increased PKA activity in the VTA. Additionally, all three drugs elevated the activity of the Akt–GSK3β signalling pathway in a time-dependent manner, while only aripiprazole stimulated the Dvl-3–GSK3β–β-catenin signalling pathway in the SN. Furthermore, chronic administration with both aripiprazole and haloperidol decreased the expression of NMDA receptors.

Conclusion: This study suggests that activating PKA- and GSK3β-mediated pathways and down-regulating NMDA receptor expression in the ventral midbrain might contribute to the clinical effects of antipsychotics.

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POSTER SESSION 1

P003

PARKINSON'S DISEASE WITH DEMENTIA IS ASSOCIATED WITH MORE SEVERE LOCUS COERULEUS PATHOLOGY COMPARED TO THOSE WITHOUT DEMENTIA

Benjamin Huynh*, Glenda Halliday, Yuhong Fu , James M. Shine

Brain and Mind Centre and Central Clinical School, The University of Sydney, NSW 2006, Australia

bhuy5324@uni.sydney.edu.au

Aims: To determine whether PD patients with dementia have more severe locus coeruleus (LC) pathology than those without dementia and healthy age-matched controls.

Methods: Post-mortem brains were collected with informed consent through regional brain donor programs and fixed in formalin. Three levels of the LC (rostral, intermediate and caudal) were sectioned from paraffin-embedded tissue blocks. LC neurons containing noradrenaline (NA)-associated (tyrosine hydroxylase) and pathological (alpha-synuclein, phosphorylated-tau) proteins were identified using immunohistochemistry. The number of NA+ neurons and pathological load were then quantified. The study was approved by the Human Ethics Committee at the University of Sydney.

Results: PD patients with dementia had greater amounts of alpha-synuclein pathology and a more substantial reduction in the number of NA+ neurons at the caudal LC level than PD individuals without dementia (which had significant NA+ neuronal loss (p-value <0.001) and alpha-synuclein (p-value <0.001) LC pathology compared with controls). The increased alpha-synuclein pathological load in the LC negatively correlated with the number of NA+ neurons indicating a neurotoxic relationship (r = -0.4028/p-value <0.001).

Conclusions: These findings suggest that the severity of LC pathology (alpha-synuclein accumulation and caudal NA+ neuron loss) is elevated in PD with dementia compared to those without (which also present significant LC pathology compared to controls, confirming previous literature). This may indicate that there is a similar preclinical loss of and terminal compensation by NA+ neurons in PD with dementia compared to the loss observed in the midbrain dopaminergic neurons prior to the onset of motor symptoms.

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POSTER SESSION 1

P004

MOUSE MODEL OF MYOCLONUS EPILEPSY AND ATAXIA DUE TO A MUTATION IN KCNC1 POTASSIUM CHANNEL GENE

Snezana Maljevic, Nikola Jancovski, Christopher A Reid, Steven Petrou

The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, Australia

snezana.maljevic@florey.edu.au

Aims: Progressive myoclonus epilepsy is a neurological disorder presenting with seizures, myoclonus, ataxia, and gradual neurological decline. One of its forms was recently described as myoclonus epilepsy and ataxia due to potassium channel mutation (MEAK). MEAK is caused by a recurrent de novo mutation in KCNC1, R320H. KCNC1 encodes the voltage-gated potassium channel Kv3.1, highly expressed in fast spiking interneurons and cerebellum. The aim of this study is to explore the impact of the R320H mutation and the related disease mechanisms in a knock-in mouse model carrying the corresponding alteration in the Kcnc1 gene.

Methods: Mouse model was generated using CRISPR/Cas9 technique. We assessed seizure phenotype, performed electroencephalographic (EEG) analysis and tested homo- and heterozygous mice for ataxia.

Results: Heterozygous Kcnc1RH/+ mice do not show spontaneous seizures or other apparent behavioural changes before the age of 6 months. At that time, EEG analysis in these mice revealed presence of spikes and spike and wave discharges. Severe ataxia was seen in all, and some mice developed seizures. Homozygous mice have a shorter life span and are smaller in size than wild type or heterozygous littermates. EEG recorded in these mice showed abundant presence of spikes. Increased susceptibility to pentylenetetrazol-induced seizures was found for both homo- and heterozygous mice. Only the homozygous animals showed lower threshold for thermally-induced seizures.

Conclusions: These data demonstrate that mice carrying the R320H mutation recapitulate several features of MEAK. Ongoing studies are looking into the cellular and network mechanisms underlying the observed in vivo phenotypes.

P005

HACE1 DEFICIENCY LEADS TO STRUCTURAL AND FUNCTIONAL NEURODEVELOPMENTAL DEFECTS

Vanja Nagy[1,2], Ronja Hollstein[3], Tsung-Pin Pai[1], Michel K. Herde[4], Pisanu Buphamalai[13], Paul Moeseneder[1], Ewelina Lenartowicz[2], Anoop Kavirayani[1], Georg Christoph Korenke[11], Ivona Kozieradzki[1], Roberto Nitsch[1,6], Ana Cicvaric[5], Francisco J. Monje Quiroga[5], Matthew A. Deardorff[7], Emma C. Bedoukian[7], Yun Li[8], Gökhan Yigit[8], Jörg Menche[13], E. Ferda Perçin[12], Bernd Wollnik[8], Christian Henneberger[4,9,11], Frank J. Kaiser[3] and Josef M. Penninger[1]*

1IMBA, Institute of Molecular Biotechnology of the Austrian Academy of Sciences, VBC – Vienna BioCenter Campus, Dr. Bohr-Gasse 3, 1030 Vienna Austria;
2Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases, 1090 Vienna, Austria;
3Section for Functional Genetics at the Institute of Human Genetics, University of Lübeck, Lübeck, Germany;
4Institute of Cellular Neurosciences, University of Bonn Medical School, 53127 Bonn, Germany;
5Department of Neurophysiology and Neuropharmacology, Center for Physiology and Pharmacology, Medical University of Vienna, Austria;
6Drug Safety and Metabolism, IMED Biotech Unit, AstraZeneca, Gothenburg, Sweden;
7Division of Genetics and the Roberts Individualized Medical Genetics Center, Children's Hospital of Philadelphia;
Departments of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, 19104 USA;
8Institute of Human Genetics, University Medical Center Göttingen, Göttingen, Germany;
9Institute of Neurology, University College London, WC1N 3BG London, United Kingdom;
10German Center for Neurodegenerative Diseases (DZNE), 53127 Bonn, Germany;
11Zentrum für Kinder- und Jugendmedizin, Neuropädiatrie, Klinikum Oldenburg, Oldenburg, Germany;
12Department of Medical Genetics, Faculty of Medicine, Gazi University, 06500 Ankara, Turkey;
13CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Lazarettgasse 14 AKH BT25.3, 1090 Vienna, Austria

vanja.nagy@lbi.lbg.ac.at

HECT Domain and Ankyrin Repeat Containing E3 Ubiquitin Protein Ligase (HACE1) was initially identified in Wilm's tumor, and subsequently characterized as a tumor suppressor. Recently, mutations in HACE1, were shown to be associated with an autosomal recessive neurodevelopmental syndrome called Spastic Paraplegia and Psychomotor Retardation with or without Seizures (SPPRS; OMIM#616756). The causality and molecular and functional underpinnings of HACE1-deficiency in neurodevelopment are not known.

Here, we identify two novel homozygous truncating mutations in HACE1 in three patients from two families, p.Q209* and p.R332*, with similar symptoms as those previously reported for SPPRS.

To gain insight into the molecular pathophysiology of SPPRS, we performed detailed molecular and phenotypic analyses of hace1 knock-out (KO) mice and SPPRS patient fibroblasts.

We show that hace1 KO mice display many clinical features of SPPRS including enlarged ventricles, hypoplastic corpus callosum, as well as locomotion and learning deficiencies. Mechanistically, loss of HACE1 results in altered abundance and activity of the small GTPase, RAC1, and a loss of hippocampal spine number, which presumably undelies abrogated long-term potentiation (LTP). Similarly, in fibroblasts from SPPRS patients, carrying disruptive HACE1 mutations, resembling loss of HACE1 in the KO mice, we observed significant upregulation of the total and active, GTP-bound, form of RAC1, along with an induction of RAC1-regulated downstream pathways.

Our results provide a first animal model to dissect this complex human disease syndrome, establishing the first causal proof that a hace1 mutation results in altered synapse formation and structural and behavioral neuropathological features that resemble SPPRS patients.

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P006

HOW CAN ANTI-GAD65 ANTIBODIES AFFECT LEARNING AND MEMORY IN MICE?

Laurence Ris, Agnès Villers and Célestine Brunois

Department of Neuroscience, Health Research Institute, University of Mons, Mons, Belgium

laurence.ris@umons.ac.be

Aims: Anti-glutamate decarboxylase 65 (GAD65) antibodies are detected in patients suffering from various neurological pathologies including some with cognitive deficits. This study tends to explore the impact of two anti-GAD65 epitope-specific antibodies (b78 and b96.11) in the hippocampus.

Methods: For this purpose, the animal model developed consists to implant a cannula into the third cerebral ventricle, connected to an osmotic pump. It allows delivering slowly antibodies during three days after the stereotactic surgery. The antibodies diffusion into the brain and inside neurons was characterized thanks to a fluorescent labeling. Then, electrophysiological measures were performed to study the long-term potentiation of the synaptic response in the Ammon's horn while immunochemistry and ELISA were used to assess neuroinflammation.

Results: We showed a significant decrease in LTP in mice treated with b78 antibodies compared to groups with b96.11 or sham, a proliferation of microglia and astrocytes and an increase in cytokine release in mice treated with b78 and b96.11. Moreover, a cognitive deficit was revealed by contextual fear conditioning and Morris water maze test and a decrease of the expression of different subunits of glutamate receptors was highlighted by western blotting in treated mice.

Conclusions: All these results suggest that GAD65-specific antibodies impaired synaptic plasticity and memory in relation to the induction of an inflammatory state in the hippocampus.

We thank the Professor Hampe of the University of Washington to having supplied anti-GAD65 antibodies. Célestine Brunois is a recipient of a FRIA fellowship.

P007

NEMATODE CAENORHABDITIS ELEGANS AS ANIMAL MODEL FOR STUDYING PATHWAYS UNDERLYING SCHIZOPHRENIA: IMPACT OF NUCLEAR DISTRIBUTION ELEMENT GENES IN THE RESPONSE TO TYPICAL AND ATYPICAL ANTIPSYCHOTICS

João V. Nani[1], Gabriela Guilherme Monte[1], Caroline Dal Mas[1], Lucas Gelain Martins[2], Ljubica Tasic[2], Marcelo A. Mori[3], Mirian A. F. Hayashi[1]

1Department of Pharmacology, Escola Paulista de Medicina (EPM), Universidade Federal de São Paulo (UNIFESP) São Paulo, Brazil;
2Chemical Biology Laboratory, Department of Organic Chemistry, Institute of Chemistry, Universidade Estadual de Campinas (Unicamp), Campinas, SP, Brazil;
3Departamento of Biochemistry and Tissue Biology, Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil

mhayashi@unifesp.br

Aim: The nematode Caenorhabditis elegans expresses the nuclear distribution element genes nud-1 and nud-2 demonstrated to be the worm homolog of the mammalian NDE1 and NDEL1. NDE1 and NDEL1 share overlapping roles in brain development in mammals and they are the main binding partners of the Disrupted-in-Schizophrenia (DISC1), a susceptibility gene for schizophrenia (SCZ). NDEL1 enzyme activity is significantly lower in treatment resistant SCZ subjects compared to non-resistant patients, who essentially presented response to the therapy with the atypical antipsychotic clozapine but not with typical antipsychotics. We aim to clarify the possible NDEL1 roles in the response to treatment, and evaluate its correlation with rodent animal model and clinical evidences.

Methods: Null-knockout worms for nud-1 and nud-2 were used to evaluate the effect(s) of the intervention with typical and atypical antipsychotics on behavioral and biochemical responses in the absence of these genes.

Results: Analysis of worm behaviors, modulated by the dopaminergic and/or serotoninergic pathways, suggested an important unbalance in serotonin pathways in both knockout worms, which is in line with previous studies with rodent animal models and clinical evaluations with SCZ patients. 1H HR-MAS NMR spectra showed an interesting trend to make similar the metabolic profile of mutant knockout worm to wild-type animals after the treatment with antipsychotics.

Conclusion: The present data provide new insights to understand the roles of these genes in the response to the pharmacotherapy with antipsychotics. In addition, this experimental animal model is a valuable tool to explore the convergence between dopamine/serotonin pathways and neurodevelopmental processes.

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P008

EVALUATION OF THE ANTIPSYCHOTICS' EFFECTS ON LIPIDS IN RAT STRAINS

Danijela Stanisic[1], Joao Victor Silva Nani[2], Banny Silva Barbosa Correia[1], Ranieri W. Ricardo[1], Tassia Brena da Costa[1], Mirian Akemi F. Hayashi [2], Ljubica Tasic [1]

1Instituto de Química, Universidade Estadual de Campinas, Campinas-SP, Brazil;
2Departamento de Farmacologia, Escola Paulista de Medicina (EPM), Universidade Federal de São Paulo (UNIFESP), Sao Paulo, Brazil

stanisicdanijela@yahoo.com; mhayashi@unifesp.br; ljubica@unicamp.br

Aims: To evaluate effects of psychotic drugs on serum lipidome in animal models and link the observed results with the possible molecular processes occurring in the human body after medication. We compered the effects of the atypical antipsychotic drug – clozapine, which is the first choice to treat treatment-resistant schizophrenia patients, with the effects of the most widely employed typical antipsychotic – haloperidol.

Methods: The Spontaneously Hypertensive Rats (SHR, n = 5), and Wistar Rats (WR, n = 5) were treated for 30 days with haloperidol (n = 5), clozapine (n = 5), or with vehicle (n = 5). Serum lipids were extracted and their ^{1}H NMR spectra were recorded using 600 MHz Bruker *AVANCE III* spectrometer. NMR spectral data were analyzed using chemometrics.

Results: Lipidomics by NMR have shown that clozapine caused fewer changes in lipids compared to haloperidol in both animal strains. Clozapine and haloperidol provoked several variations in the signals of various lipids in WR, especially in regions of low density and very low-density lipoproteins. On the other hand, lipidomes of SHR treated with clozapine and haloperidol showed alterations in NMR regions of olefinic protons acyl group from polyunsaturated fatty acids and glyceryl group proton on C2 from phospholipids or triglycerides.

Conclusion: SHR did not suffer from same serum lipid alterations when compared to WR under drugs. Therefore, metabolic effects of the antipsychotic drugs depended on animal model used and were not uniform. Our data bring new insights into metabolic syndrome frequently associated to prolonged therapies with antipsychotic drugs.

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P009

BENFOTIAMINE REVERSE THE MEMORY-RELATED DEFICITS BY MODULATION OF BRAIN INSULIN SIGNALING AND INFLAMMATION IN AN EXPERIMENTAL MODEL OF SPORADIC ALZHEIMER'S DISEASE

Torrão A.S. & Moraes R.C.M.

Dept. Physiology and Biophysics, Institute of Biomedical Sciences, University of São Paulo, São Paulo, SP, Brazil

andrea@icb.usp.br

Aims: Studies suggest that disturbances in glucose metabolism, insulin signaling and mitochondrial function in the brain are associated with the early stages and progression of Alzheimer's disease (AD). This study aimed to evaluate the effects of 30 days of benfotiamine (B) supplementation (analogue of thiamine), which is related to metabolism and mitochondrial function, in an experimental model of AD in rats, produced by intracerebroventricular injection of streptozotocin (STZ).

Methods: Wistar rats, subdivided into the following groups: CTL, CTLB, STZ, and STZB, were evaluated after supplementation for their cognitive performance in the object recognition behavioral test and for biochemical and molecular parameters.

Results: Benfotiamine increased the thiamine diphosphate concentrations in the hippocampus of CTLB and STZB groups ($p=0.0005$) compared to non-supplemented groups, and was able to improve the discrimination index in both short-term (75.54%, $p=0.0009$) and long-term (44.35%, $p=0.001$) memories compared to STZ group. Benfotiamine produced an increase (55.79%, $p=0.05$) in the insulin receptor phosphorylation (Tyr1150/1151) of STZB group compared to the STZ group, and increased (70.64%, $p=0.05$) the GSK-3 phosphorylation (Ser21/9) in the STZB group compared to all other groups. On the other hand, CTLB and STZB groups had lower (43.91%, $p=0.03$ and 47.63%, $p=0.02$, respectively) phosphorylation of MAPK (Thr202/Tyr204ERK1/2) compared to CTL group. Benfotiamine was also able to reverse (44.55%, $p=0.03$) the increased expression of Glial Fibrillary Acidic Protein (GFAP) induced by STZ.

Conclusions: Our data indicate that benfotiamine supplementation was able to reverse the memory-related deficits produced by STZ, by modulation of hippocampal insulin signaling and inflammation.

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P010

GC-MS UNTARGETED ANALYSIS IN POSTTRAUMATIC STRESS DISORDER

Marcela Konjevod[1,2], Jorge Saiz[2], Matea Nikolac Perkovic[1,2], Gordana Nedic Erjavec[1], Lucija Tudor[1], Coral Barbas[2], Neven Zarkovic[3], Dubravka Svob Strac[1], Nela Pivac[1]

1Rudjer Boskovic Institute, Department of Molecular Medicine, Laboratory for Molecular neuropsychiatry, Zagreb, Croatia;
2The Centre of Metabolomics and Bioanalysis (CEMBIO) at the Pharmacy Faculty, University San Pablo CEU, Madrid, Spain;
3Rudjer Boskovic Institute, Department of Molecular Medicine, Laboratory for Oxidative Stress, Zagreb, Croatia

mkonjev@irb.hr

Aims: Posttraumatic stress disorder (PTSD) is a stress and trauma-related disorder characterized with a typical clusters of symptoms. The exact neurobiological background and molecular basis of this complex and severe psychiatric disorder is still unclear. Therefore, the aim of this study was to determine the specific metabolites as potential biomarkers in PTSD development and progress.

Methods: Gas chromatography coupled with mass spectrometry was used to determine metabolites that differ between plasma samples of 50 PTSD subjects and 50 healthy controls. Prior to untargeted analysis on GC (Agilent 7890A)-Q-MS (Agilent 5975C), samples were prepared using protein precipitation in cold acetonitrile, followed by methoximation with O-methoxamine hydrochloride in pyridine and silylation using N,O-bis (trimethylsilyl) trifluoroacetamide (BSTFA).

Results: Obtained chromatograms were processed and data was normalized according to tricosane (internal standard). After data treatment and exclusion of metabolites with percentage of relative standard deviation (%RSD) higher than 30%, statistical analysis was conducted. Depending on data normality, t-test or Mann-Whitney test were performed, followed by Benjamini-Hochberg correction. Fifteen significantly different compounds ($p>0.05$) were obtained after statistical analysis. Identified compounds belong to the groups of sugars, organic acids, amino acids or their derivatives.

Conclusions: PTSD is a multifactorial and systemic stress-related disorder, which development and progression include several metabolic and signaling pathways. Therefore, it is not surprising that some of the significantly altered metabolites in PTSD are associated with stress. Future studies are necessary to further investigate and enlighten possible role of these metabolites in the development of PTSD.

P011

EFFECTS OF GUANYLATE CYCLASE-C ON BRAIN ISCHEMIC LESION FORMATION

Martina Ratko[1,3], Nikola Habek[1,2,3], Marina Dobrivojević Radmilović[1], Siniša Škokić[1], Helena Justić[1], Aleksandra Dugandžić[1,2,3]

1Croatian Institute for Brain Research, School of Medicine, University of Zagreb, Šalata 12, Zagreb, Croatia;
2Department of Physiology and Immunology, School of Medicine, University of Zagreb, Šalata 3, Zagreb, Croatia;
3Centre of Excellence for Basic, Clinical and Translational Neuroscience, School of Medicine, University of Zagreb, Šalata 12, Zagreb, Croatia

martina.ratko@mef.hr

Aims: Agonists of guanylate cyclase (GC) A but not GC-B are reducing the size of the brain lesion after an ischemic stroke. The aim of this study is to show if GC-C is involved in development of ischemic stroke.

Methods: Middle cerebral artery occlusion (MCAO) was performed in wild type (WT) and GC-C knock-out (GC-C KO) mice. The volumes of brain lesions were determined 24h and 7 days after MCAO by MRI. In addition, patch clamp experiments and immunohistochemistry were performed.

Results: Twenty-four hours after MCAO, GC-C KO animals have decreased lesion volumes compared to WT mice (WT:121±12 mm3, GC-C KO:79±14 mm3). Even though we showed a reduction in brain lesion 7 days after MCAO in WT mice, there was no change in GC-C KO mice and differences between mice were not present. Furthermore, GC-C agonist, uroguanylin, hyperpolarized cerebellar Purkinje neurons, (-7.2±1.4mV, n=5) while this effect was abolished in GC-C KO mice (1.6±1.7mV, n=4). Since most of the ischemic lesion of our mouse model is located in the cerebral cortex, it is not surprising that GC-C is present in neurons of cerebral cortex.

Conclusion: Effects of GC-C activation on ischemic stroke are opposite to effects of GC-A agonists. GC-C KO mice develop smaller lesion volume 24h but not 7 days after an ischemic stroke compared to WT mice suggesting the possible benefit of specific GC-C inhibitors in treatment of ischemic stroke.

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P012

SINGLE NUCLEOTIDE VARIANTS ASSOCIATED WITH THE CARDIAC ARRHYTMIAS IN PATIENTS WITH EPILEPSY

Ioanna Kousiappa[1], Maria Pechlivanidou[2], Savvas S. Papacostas[1,2]

1 Neurology Clinic B, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus;
2The Cyprus School of Molecular Medicine, Nicosia, Cyprus

ioannak@cing.ac.cy

Aims: Epilepsy is a complex brain disorder defined by recurrent unprovoked seizures that are characterized as excessive neuronal activity due to synchronous neuronal excitation. People with epilepsy have an increased risk of having sudden death in epilepsy (SUDEP). The genetic association of Epilepsy and SUDEP is poorly explained. Genes implicated in cardiac arrhythmias, like the Long QT (LQTS), short QT (SQTs) and Brugada syndromes, Sudden Cardiac Death (SCD) are genes associated with SUDEP risk. The aim was to detect known single nucleotide variants (SNVs) in cardiac arrhythmias genes in patients with genetic generalized epilepsy.

Methods: A genotypic analysis was conducted in specific coding regions of cardiac arrhythmias genes, SCN5A, KCNQ1, KCNH2, KCNE1, KCNJ2, SCN1B and HCN4, with Sanger Sequencing in 58 patients with generalized tonic-clonic seizures and 31 controls with no history of epilepsy. Three of the patients had a family history of SUDEP and four patients were not responsive to the antiepileptic drugs, thus at clinical level were at high risk of SUDEP.

Results: Known SNVs with minor allele frequencies from 0.1% to 22% were detected in the studied genes of the patients (25 patients had one SNV, 16; two, 5; three and 1; five), but not the controls. The variants were associated with all cardiac arrhythmia's syndromes.

Conclusions: Further research must be conducted in SUDEP families focusing on the role of those variants in the pathophysiology of SUDEP, Epilepsy and cardiac arrhythmia. The long-term outcome would be the identification of specific variants as possible genetic prevention SUDEP markers.

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P013

REDUCED HIPPOCAMPAL ACTIVITY DURING STEREOTYPICAL CHECKING IN ANIMAL MODEL OF OBSESSIVE-COMPULSIVE DISORDER (OCD) INDUCED BY QUINPIROLE SENSITIZATION

Hana Brozka[1], Dominika Radostova[1], Daniela Alexova[1], Stepan Kubik[1], Branislav Krajcovic[1], Jan Svoboda[1], Ales Stuchlik[1]

1Institute of Physiology of the Czech Academy of Sciences, Prague, Czechia

hana.hatalova@fgu.cas.cz

Aims: Obsessive-compulsive disorder is a serious psychiatric disease characterized by repeated intrusive thoughts (obsessions) often followed by physical and/or mental acts (compulsions) which offer temporal relief to a patient. Presently, neurobiological substrate of checking behavior is not completely understood.

Methods: We utilized compulsive checking following sensitization to quinpirole (QNP; a dopamine D2/D3 agonist). For the 10 sessions rats were administered quinpirole (n = 13) or saline (n=14) and placed into enriched openfield (50min). Visits to objects and corners were recorded. After last session, rats were sacrificed for in-situ hybridization of Arc mRNA. We determined activity of cortical regions implied in OCD. Namely we assessed Arc expression in orbitofrontal cortex, anterior cingulate cortex, medial prefrontal cortex) and in hippocampus (CA1, CA3 and dentate gyrus).

Results: We observed a development of checking behavior during QNP sensitization and observed a stable pattern of visiting frequencies of arena locations. Compared to previous studies our analysis is more complex and confirms session-to-session stability of checking. Moreover, we found severely reduced activity in all hippocampal regions (10% of CTR , $p<0.001$), but no difference in regions implied in OCD (dACC, OFC, mPFC, all $p<0.05$).

Conclusions: Hippocampal hypo-activation during checking is interesting, because behavioral similarity between the sessions intuitively implies memory of previous session. Hippocampus is a region important in memory formation; but it appears that it is not necessary in formation of all long-term memories.

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P014

SLEEP INTEGRATES RAPID ANTIDEPRESSANT MECHANISMS

Kohtala S, Rantamäki T

Laboratory of Neurotherapeutics, Division of Pharmacology and Pharmacotherapeutics, Faculty of Pharmacy, and SleepWell Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland

samuel.kohtala@helsinki.fi

Aims: Rapid antidepressant effects are often connected to neurobiological alterations ingeniously controlled by the drug while the active involvement of neural networks in the process is undervalued. We sought to formulate a hypothesis that better accounts for the complexity of depression and provides a novel explanation for rapid antidepressant effects.

Methods: While pharmacological action is essential for any drug effects, we reason that the core of rapid antidepressant effects largely depend on homeostatic adaptations triggered within the brain in response to a pharmacological challenge, and its consecutive release. After reviewing the scientific literature with this in mind, we found exciting similarities with rapid antidepressant effects and mechanisms of memory and sleep.

Results: Our synaptic hypothesis of renormalization in depression (SHRED) proposes that in vulnerable individuals, susceptible neuronal networks gradually become hyper/hypoactive under predisposing developmental and environmental conditions. This results in dysfunctional brain states and manifest as e.g. uncontrollable self-focused rumination and cognitive dysfunction. Rapid-acting antidepressants produce robust synaptic potentiation leading to the re-emergence of rich global-level functional connectivity, and amelioration of symptoms. Connectivity changes are accompanied by transiently increased synaptic strength along with the homeostatic emergence of slow-wave activity (SWA) after the acute pharmacological effects subside. During SWA, synaptic downscaling takes place, but the preceding excitation offers protection from renormalization in previously hypo-potentiated networks. If no further therapy is applied, susceptible neuronal networks regain abnormal activity during several subsequent wake-sleep cycles and the relative potentiation is lost.

Conclusions: SHRED offers a novel framework for explaining and examining rapid antidepressant effects.

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P015

THE EFFECT OF DEEP-BRAIN STIMULATION OF THE MEDIAL FOREBRAIN BUNDLE ON SLEEP IN THE FSL RAT MODEL OF DEPRESSION

Wilf Gardner[1,2], Laura Durieux[1], Fanny Fuchs[3], Chantal Mathis[1], Volker Arnd Coenen[2], Jorge Mendoza[3], Máté Döbrössy[2], Lucas Lecourtier[1]

1Laboratoire de Neurosciences Cognitives et Adaptatives, Université de Strasbourg;
2Department of Stereotactic and Functional Neurosurgery, Universitätsklinikum Freiburg;
3Institut des Neurosciences Cellulaires et Intégratives, Université de Strasbourg

wilf.gardner@uniklinik-freiburg.de

Aims: The biological mechanisms of Major Depressive Disorder (MDD) are poorly understood, and sleep-related symptoms represent an important facet of this. A sizeable subset of MDD patients are treatment-resistant, necessitating novel approaches. Pre-clinical and clinical studies on deep-brain stimulation (DBS) of the medial forebrain bundle (MFB) to treat MDD are currently ongoing. The Flinders Sensitive Line (FSL) rat is a model for depressive symptoms, including some sleep deficits. In the current study, the extent of sleep and circadian rhythm deficits in the FSL, and the effects of MFB-DBS on various factors relating to sleep, were investigated.

Methods: Depressive-like FSL and non-depressive Sprague Dawley (SD) rats received ECoG, EMG, medial prefrontal cortex, nucleus accumbens and CA1 hippocampus electrode implantations. Recordings were conducted pre-and post- 24 hours MFB-DBS. A depressive-like behavioural phenotype was assessed using the forced swim test. Post-mortem, expression of clock genes and melatonin was examined using in situ hybridisation and ELISA respectively.

Results: FSLs exhibited differential sleep architecture and oscillatory activity compared to SDs. After MFB-DBS, a significant reduction in the depressive-like behavioural phenotype was observed, but no significant changes in measures associated with sleep. Analysis of clock gene and melatonin expression is ongoing.

Conclusions: Results confirm sleep symptoms described previously in the FSL, and suggest phenomena present in oscillatory communication between regions. This may represent a mechanism connected to sleep symptoms or an unrelated phenotype. Post-stimulation results suggest an antidepressant-like effect of MFB-DBS on behaviour, but no significant effect on sleep symptoms.

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P016

DIFFERENTIAL SUSCEPTIBILITY OF HIPPOCAMPAL NEURONS IN SLICE CULTURES TO HEAT SHOCK

Eckart Förster,Shaleen Rana, Jasmin Weninger, Anne-Kathrin Trampe, Maurice Meseke

1Department of Neuroanatomy and Molecular Brain Research Ruhr-University of Bochum, Bochum, Germany

eckart.foerster@rub.de

Hippocampal slice cultures are a well established in vitro model to study development, function and plasticity of hippocampal neurons during health and disease in a tissue context that is similar to the in vivo situation.

Here, we used hippocampal slice cultures to study the susceptibility of different hippocampal neuronal cell types to heat shock.

Thus, to simulate a fever situation in vitro, the incubation temperature for the slice cultures was increased to 41 °C for a period of several hours. Afterwards, the slice cultures were again incubated at 37°C for several days, stained with propidium iodide (PI) to evaluate cell viability, and subsequently fixed with paraformaldehyde. The slice cultures were then immunohistochemically stained with antibodies against cell type specific marker proteins, including Prox-1, a marker protein for dentate granule cells, and Reelin, which is expressed by Cajal-Retzius cells. Cell type specific damage was quantified by assessing the ratio of PI-positive and PI-negative cells.

Our results suggest that in particular principal neurons, i.e. dentate granule cells and pyramidal neurons, are susceptible to damage by heat shock, while Cajal-Retzius cells are unaffected.

In future experiments we want to take advantage of this in vitro model to explore molecular mechanisms that underlie the differential susceptibility of different hippocampal neuronal cell types to heat shock, in particular mechanisms that protect against damage of some neuronal cell types, such as Cajal-Retzius cells.

P017

PHARMACOLOGICAL BLOCKADE OF ABCB1 AND ABCC1 TRANSPORTERS HAS NO DELETERIOUS EFFECT ON BRAIN ISCHEMIC STROKE OUTCOME

Maryam Sardari, Daniel Manrique Castaño, Tayana Silva de Carvalho, Christoph Kleinschnitz, Dirk M. Hermann

Department of Neurology, University Hospital Essen, Essen, Germany

sardari_89@yahoo.com

ATP-binding cassette (ABC) transporters ABCB1 and ABCC1 expressed on the brain capillary endothelium actively regulate blood-brain barrier permeability and limit drug uptake in the ischemic brain tissue during acute phase post-stroke. In contrast to studies on Alzheimer or Parkinson diseases which claimed that long-term inhibition of ABCB1 and ABCC1 transporters exacerbated the brain injury, up to now little attention has been paid to the effects of this treatment on brain ischemic stroke.

Therefore, in this study we investigated the influence of the selective long-term pharmacological inhibition of these transporters on stroke outcome. Male C57Bl6 mice were exposed to 30 min transient intraluminal middle cerebral artery occlusion. They received the ABCB1 inhibitor tariquidar (8 mg/kg/day) or the ABCC1 inhibitor MK-571 (10 mg/kg/day) alone or in combination over up to 28 days post ischemia (dpi).

Here we show that treatment with either inhibitors alone or in combination did not have a detectable effect on stroke parameters such as the brain volume, striatal volume and the corpus callosum thickness after 14, 28 and 42 dpi. Furthermore, weekly neurological scoring, rotarod, tight-rope and open-field tests demonstrated that post ischemic motor coordination deficits were not influenced by the drug treatment in any of experimental settings.

Overall, we demonstrate that deactivation of single ABCB1 or ABCC1 transporter or their simultaneous blockade does not have any unfavorable effects on neurological recovery and brain remodeling. Our results suggest that inhibition of these transporters may be used to enhance the accumulation of plasticity promoting drugs in the ischemic brain.

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P018

MOUSE MODEL OF SPORADIC CREUTZFELDT-JAKOB DISEASE RESEMBLES REGIONAL AND SUBTYPE-DEPENDENT MIRNA SIGNATURES

Katrin Thüne[1,*], Franc Llorens[2,*], Eulàlia Martí[3], Matthias Schmitz[1], Nadine Gotzman[1], Margarita Carmona[4], Uwe Michel[1], Olivier Andréoletti[5], José Antonio del Río[2,6,7], Juana Díez[8], Juan Carlos Espinosa[10], Juan Maria Torre[9], Isidre Ferrer[5,2#], Inga Zerr[1,10,#]

1Department of Neurology, University Medical School, Göttingen, Germany;
2CIBERNED (Network center for biomedical research of neurodegenerative diseases), Institute Carlos III, Ministry of Health, Spain;
3Centre for Genomic Regulation, Barcelona, Spain;
4Institute of Neuropathology, IDIBELL-University Hospital Bellvitge, Barcelona, Spain;
5Institut National de la Recherche Agronomique/Ecole Nationale Vétérinaire, Toulouse, France;
6Molecular and Cellular Neurobiotechnology, Catalonian Institute for Bioengineering (IBEC), Parc Científic de Barcelona, Barcelona, Spain;
7Department of Cell Biology, University of Barcelona, Barcelona, Spain;
8Department of Experimental and Health Sciences, Universitat Pompeu Fabra, 08003 Barcelona, Spain;
9 Centro de Investigación en Sanidad Animal (CISA-INIA), Madrid, Spain;
10German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany

*These authors equally contributed to this work; #These authors share senior authorship

k.thuene@hotmail.com

Prion diseases are a group of incurable progressive neurodegenerative disorders including sporadic Creutzfeldt-Jakob disease (sCJD) in human. Straightforward links have been established between neurodegenerative diseases and miRNA deregulated patterns. We demonstrated global miRNA expression alterations in sCJD affected brain regions that are highly changed in a regional and disease subtype-dependent manner.

A major goal of following investigations was to dissect to what extent miRNA alterations are resembled in a CJD mouse model. Therefore, we systematically mapped miRNA expression alterations during disease progression in a cell- and regional-dependent manner by a combination of miRNA profiling approaches via qPCR technique and miRNA in situ hybridization assays.

Our work clearly demonstrates that the altered miRNA expression signatures in sCJD are resembled in the CJD mouse model. We successfully validated expression changes of ten and eleven miRNAs via qPCR technic in the cortex and in the cerebellum of the CJD mouse model during clinical stages. Temporal miRNA expression analysis from the CJD mouse revealed that the alterations mainly occur with the onset of symptoms, suggesting that the pool of analyzed miRNAs specifically alters during clinical disease stages. Among this pool, the miR-124-3p (downregulated) and miR-16-5p (upregulated) change their expression during early symptomatic phase in the CJD mice, indicating the contribution of those miRNAs in pre- and early clinical prion disease mechanisms.

This model provides an indispensable tool to study the cause-consequence relationships of miRNA dysregulation in prion disease progression and provides a unique platform to assess biomarker candidates and therapeutic targets.

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POSTER SESSION 1

P019

THE NEUROCOGNITIVE PROFILE OF DISORGANIZED SCHIZOTYPY: PRELIMINARY FINDINGS

Stella G. Giakoumaki, Peny Karamaouna, Leda Karagiannopoulou, Chrysoula Zouraraki

Department of Psychology, University of Crete, Rethymno Crete, Greece

sgiakoumaki@uoc.gr

Aims: The effects of schizotypal personality traits on neurocognition have been well documented. The highest percentage of existing studies, though, have focused on the effects of either paranoid and negative schizotypal dimensions or total schizotypal scores. The aim of the present study was to examine the effects of high disorganized schizotypy only as well as in combination with high paranoid or negative schizotypal traits on a wide range of neurocognitive functions.

Methods: Eighty-seven healthy community participants were divided into four groups according to their scores in the Schizotypal Personality Questionnaire: (a) high disorganized schizotypy (DiS, n=19), (b) high disorganized/negative schizotypy (DNS, n=16), (c) high disorganized/paranoid schizotypy (DPS, n=20) and (d) control group (zero scores in all dimensions, n=32). Participants were assessed with tasks examining planning/complex problem solving, set-shifting, information processing speed, executive working memory and attention switching. Between-group comparisons were examined with analyses of variance.

Results: There was no difference between the control and the DiS groups in any outcome measure. Both groups, however, had superior planning/complex problem solving compared with the DNS and DPS groups (all p values <0.01) and set-shifting compared with the DNS group (all p values <0.05). Only the control group outperformed the DPS group in information processing (all p values <0.05) and the DNS group in attention-switching (all p values <0.01).

Conclusions: These preliminary findings for the first time highlight the association of disorganized schizotypal traits with prefrontally-mediated neurocognitive functions. They, also, add further in the literature pertaining to protective endophenotypic markers in the schizophrenia-spectrum.

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P020

TARGETING NUCLEAR RECEPTOR NR5A2/LRH-1 IN NERVOUS SYSTEM MALIGNANCIES

Dimitrios Gkikas, Dimitrios Stellas and Panagiotis Politis

Center for Basic Research, Biomedical Research Foundation of the Academy of Athens, Greece

dimitrgkikas@gmail.com

Aims: Clinical data from TCGA and Oncomine databases, suggest that the nuclear receptor NR5A2 is down-regulated in Glioblastoma tumors as compared to healthy tissue. Here, we experimentally investigated this hypothesis, by testing whether NR5A2 and its pharmacological agonists (DLPC and DUPC) are able to inhibit glioblastoma and neuroblastoma cancer cell growth.

Methods: In order to investigate the role of NR5A2 in in Nervous System cancer cell lines we performed immunofluorescent staining. RT-qPCR western blot and luciferase assay were performed to study the molecular mechanism that underlies the antiproliferative effects of NR5A2. To study NR5A2 agonists in vivo we performed xenografts in NOD-SCID mice.

Results: Our studies showed that NR5A2 is sufficient to strongly suppress proliferation of both human and mouse neuroblastoma (SH-SY5Y, Neuro2A) and glioblastoma cells (U87-MG, GL261) without affecting apoptosis. The anti-proliferative effects of NR5A2 are mediated by the induction of negative regulators of cell cycle, p27kip1 and p21cip1, as well as Prox1, a tumor suppressor protein in neuroblastoma cells [6]. We next examined the ability of DLPC and DUPC to mimic the anti-proliferative action of NR5A2. Indeed, these agonists were able to inhibit proliferation in human glioblastoma cell line U87-MG through the induction of the previously mentioned tumor suppressors. Most importantly, treatment with DLPC reduced tumor growth in xenografts model of NOD-SCID mice.

Conclussion: These data reveal a tumor suppressor role of NR5A2 in Nervous System and render this nuclear receptor an important pharmacological target for the treatment of nervous tissue related tumors.

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P021

HFOS IN HIPPOCAMPAL CA1 IN VITRO DEPEND ON INTERICTAL DISCHARGE GENERATION MECHANISMS AND CAN BE MODIFIED BY HERBAL EXTRACTS

Kostas Kalogeropoulos[1], Dimitrios Kleidonas[1], Anastasios Troganis[2], Halarambos Stamatis[3] and Caterina Psarropoulou[1]

1Human & Animal Physiology Laboratory;
2Environmental and Physicochemical Studies Laboratory and 3Biotechnology Laboratory, Department of Biological Applications and Technology, Faculty of Health Sciences, University of Ioannina, 45110 Ioannina, Greece

kost.kalogeropoulos@gmail.com

Aim: To analyze High-frequency oscillations (HFOs) in 2 in vitro models of spontaneous Interictal discharges (IEDs) with different generation mechanisms, and any changes therein following herbal extract perfusion.

Materials-Methods: Perfusion of adult rat hippocampal slices with Mg^{2+}-free ACSF (NMDA-R activation, n=37 slices) or with 50μM 4-aminopyridine (4-AP, K^+ conductance inhibition, n=41) induced spontaneous IEDs recorded extracellularly in CA1, upon which the effects of aqueous extracts of *Salvia officinalis*, *Olea europaea*, *Ilex paraguariensis*, and *Acorus calamus were studied (all at 0.1*mg/mL*)*.

Results: Ripple and Fast Ripple duration differed significantly in the 2 models (p<0.0001), similarly to IED duration (4-AP: 0,06 ± 0,003s, Mg2+-free: 0,09 ± 0,006s, p<0.0001). The following were model dependent: Ripple amplitude (p=0.0006), delay between Ripple-IED onset (p=0.008) or Fast Ripple-IED onset (p=0.01), peak Ripple power (4-AP: 133,2 ± 5,2Hz, Mg2+-free: 147,7 ± 4,6Hz, p=0.04). *Acorus calamus reduced* Ripple amplitude in 4-AP (-1,60±0.56mV, n=5, p=0.046) and peak frequency in Mg2+-free (-12.21±2.75Hz, n=5, p=0.007). Olea europaea increased Ripple amplitude in Mg2+-free (1.71±0.60mV, n=6, p=0.0359) and Ilex paraguariensis reduced the Fast Ripple-IED onset delay in 4-AP (-0.003±0.001s, n=5, p=0.0115). Salvia officinalis did not affect HFOs. All extracts altered IED frequency, duration and/or amplitude depending on the model.

Conclusions: Significant differences between HFOs within IEDs in the two models indicate that IED activation mechanisms influence the inherent HFOs, and consequently neuronal network synchronization tendencies. Herbal extract effects on HFOs were not in concordance to those on IEDs, indicating differences in the regulatory mechanisms of IEDs and of the HFOs they contain.

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POSTER SESSION 1

P022

APPLYING TDCS IN A COGNITIVE REHABILITATION PROGRAM: DIFFERENCES OBSERVED IN FOCAL AND DIFFUSE LESIONS

Stefas Eleftherios[1], Pantzartzidou Aleksandra[1], Minaritzi Dimitra[1], Kouki Evgenia-Peristera[1,2]

1Evexia Rehabilitation Center, Nea Kallikrateia, Greece;
2Lab of Cognitive Neuroscience, Department of Psychology, Aristotle University, Greece.

e.p.kouki@gmail.com

Aims: We aimed to investigate the benefits of tDCS in patients with left/right focal brain damage and diffuse lesions.

Methods: We applied tDCS during the rehabilitation program of two patients with focal stroke-related lesions (one right and one left), and two TBI patients. We also included an age- and lesion-matched control group, who received treatment as usual. Mean age of the tDCS group was 49 (SD: 19.85), and mean age of the control group was 47 (SD: 22.55). Mean duration of hospitalization was 73.754 days for the tDCS group (SD: 58.53), and 62.75 days for the control group (SD: 38.19). Montreal Cognitive Assessment (MoCA; Nasreddine, Phillips, Bédirian, Charbonneau, Whitehead, Collin & Chertkow, 2005) for baseline and outcome measures.

Results: Non-parametric Mann-Whitney test showed statistically significant differences between the two groups (U=5, p<0.05), with participants who had received tDCS demonstrating higher performance on the outcome measure (Mean improvement: 100.75%), compared to the control group (Mean improvement: 20.32%). Within the experimental group, participants with focal lesions demonstrated quicker recovery (233%, 50%), compared to participants with diffuse lesions (90%, 30%). Age (ρ_s= 0.285, p=0.49) and duration of hospitalization (ρ_s=-0.119, p=0.78) were not associated with final cognitive outcome.

Conclusions: Our findings support the beneficial influence of tDCS on neurological patients. Future work should extensively investigate which factors maximize tDCS's influence on cognitive recovery.

P023

SUSCEPTIBILITY OF THE OCULOMOTOR NUCLEUS TO PERINATAL HYPOXIA IN HUMANS: INCREASED CELL DEATH MEDIATED BY APOPTOSIS INDUCING FACTOR.

Pagida Marianna[1,2], Konstantinidou Anastasia[3], Patsouris Efstratios[3] and Panayotacopoulou Maria[1,2]

11st Department of Psychiatry, National Kapodistrian University of Athens, Greece;
2Lab of Neurobiology and Histochemistry, University Mental Health Research Institute, Papagou, Greece;
31st Department of Pathology, National Kapodistrian University of Athens, Greece

marianna_pagida@yahoo.gr

Aims: Epidemiological studies indicated that perinatal hypoxia/ ischemia (PHI) -the main underlying mechanism for most obstetric complications- is a major risk factor for the development of neurological and psychiatric disorders later in life. Our previous studies on autopsy material from neonates with neuropathological lesions of prolonged PHI indicated a dramatic reduction of tyrosine hydroxylase expression (first and limiting enzyme of dopamine synthesis) in the dopaminergic neurons of the substantia nigra (SN) with reduction of their cellular size. The question raised was therefore, whether these observations indicate an early stage of SN degeneration or a developmental defect.

Methods: We used mesencephali from 22 autopsied neonates (total corrected age ranging from 34 to 46.5 gestational weeks) after written parental consent. We immunohistochemically studied the expression of Apoptosis Inducing Factor (AIF), the main effector protein in caspase-independent death pathway, in relation to the severity/ duration of PHI, as estimated by neuropathological criteria.

Results: Although only a limited number of dying neurons were found in the SN of the human neonate under PHI, increased incidence of neuronal death was observed in the oculomotor nucleus, which in some cases with acute PHI reached 40% of neurons.

Conclusions: Our results may represent an underlying mechanism implicated in visual impairments, including defective coordination of saccades, frequently described in individuals who survived after PHI.

This work was funded by the program “Supporting Postdoctoral Researchers” (MIS:5001552) from the State Scholarships Foundation, co-financed by the Greek State and European Social Fund.

P024

INVESTIGATING THE ROLE OF STREPTOCOCCUS AGALACTIAE SURFACE LIPOPROTEINS IN BLOOD-BRAIN BARRIER CROSSING

Papastefanaki F.[1], Segklia A.[1], Dionysopoulou D.[1], Speder P.[2], Dramsi S.[3], Miriagkou V.[4], Matsas R.[1]

1Laboratory of Cellular and Molecular Neurobiology-Stem Cells, Department of Neurobiology, Hellenic Pasteur Institute, Athens, Greece;
2Brain Plasticity in Response to the Environment, Department of Developmental and Stem Cell Biology, Institut Pasteur Paris;
3Laboratory of Biology of Gram-positive Pathogens, Department of Microbiology, Institut Pasteur Paris, France;
4Laboratory of Bacteriology, Department of Microbiology, Hellenic Pasteur Institute, Athens, Greece

fpapastefanaki@pasteur.gr

Aims: Streptococcus agalactiae (Group B streptococcus, GBS) is among the major pathogens causing neonatal meningoencephalitis. Here we investigated the mechanisms that GBS employs in crossing the blood-brain barrier (BBB). Preliminary experiments in a Drosophila model indicated a GBS surface leucine rich repeat (LRR) lipoprotein, Blr, as important for brain entry. Here we assessed a Blr mutant strain for its ability to cross the BBB and cause mortality in mice.

Methods: Adult male CD-1 mice were intravenously injected with the GBS strain NEM316, or isogenic mutant Δblr and their survival was monitored over one week whilst bacterial levels were determined in the blood and brain. To identify the route of GBS brain entry, a separate group of mice was inoculated with GBS genetically marked with GFP (GFP-GBS) and their brains were processed for immunofluorescence.

Results: The number of surviving mice in the GBS group declined gradually over one week after inoculation whereas no deaths were recorded in the Δblr group. At 6 h after inoculation the brain-to-blood ratio of bacterial levels in the Δblr group was significantly lower than in the GBS group. By 24 h bacteria of neither of the two genotypes were detected in blood; nevertheless, brain levels of Δblr were significantly lower than those of GBS. At this time GFP-GBS was detected primarily at choroid plexuses and in brain areas adjacent to the ventricles.

Conclusions: Blr lipoprotein mediates brain entry and virulence of GBS, which probably enters the brain through the epithelial "blood-cerebrospinal fluid barrier" of choroid plexuses.

We acknowledge support by: 1) the project "Infectious, autoimmune and neurodegenerative diseases: study of the pathogenetic mechanisms and development of diagnostic, prognostic and therapeutic approaches" (MIS 5002486) implemented under the "Action for the Strategic Development on the Research and Technological Sector", funded by the Operational Programme "Competitiveness, Entrepreneurship and Innovation" (NSRF 2014-2020) and co-financed by Greece and the European Union (European Regional Development Fund); 2) the project InFeSteR, GRAND PROGRAMME FÉDÉRATEUR MICROBES & BRAIN INITIATIVE, Institut Pasteur.

P025

NMDA SUBUNITS AND P62 EXPRESSION IN THE MAM16 AND NEONATAL MK-801 MOUSE MODELS OF SCHIZOPHRENIA

Maria Plataki[1,2], Klairi Chalkiadaki[3], Vasiliki Nikoletopoulou[2], Kyriaki Sidiropoulou[1,2]

1Dept of Biology, University of Crete, Heraklion, Greece;
2Institute of Molecular Biology and Biotechnology-Foundation for Research and technology Hellas, Heraklio, Greece;
3Center for Discovery Brain Sciences, The University of Edinburgh, Edinburgh, UK

maria_plataki@hotmail.com

Aim: Schizophrenia has been associated with increased oxidative stress and reduced synaptic function. Recent studies have also suggested a connection between schizophrenia and autophagy impairments. Here, we investigated the expression of NMDA receptor subunits, NR2A and NR2B, which are important for synaptic plasticity and p62, a protein implicated in the autophagy process, in prefrontal cortex(PFC) and hippocampus(HPC) of MAM16, a model developed in our lab, and the neonatal MK-801(nMK-801) mouse models of schizophrenia.

Methods: Pregnant C57Bl/6J females received an i.p. injection of methylazoxymethanolacetate(MAM) (22mg/kg) or saline on gestation day 16. For the nMK-801 model, C57Bl/6J male and female mice were injected with 0.1 mg/kg MK-801 or saline, once-a-day, during postnatal day(p) 11-15. MAM16 and saline-treated PFC and HPC was isolated at p40 and p90 and from adult(p90) nMK-801-treated mice. PFC and HPC were subjected to western blot analysis for NR2A/NR2B and p62 proteins.

Results: NR2A and NR2B protein levels were significantly reduced in adult HPC and PFC of MAM16 and nMK-801 mice, compared to their respective controls. Furthermore, reduced NR2A and NR2B levels were found in adolescent PFC. On the other hand, p62 was significantly increased in the PFC and HPC of adult MAM-16 and nMK-801-treated mice, as well as in the PFC of adolescent MAM-16 compared to controls.

Conclusion: Our results indicate decreased autophagy and reduced NMDA receptor expression in two different animal models of schizophrenia in adulthood, but also in adolescent MAM16-treated mice. Thus, synaptic function and autophagy deficits are evident before the onset of behavioral deficits.

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POSTER SESSION 1

P026

CLINICAL AND IMMUNOLOGICAL STUDIES IN A 3-GENERATION FAMILY MEMBERS WITH VERY-HIGH TITERS OF ANTI-GAD ANTIBODIES

Tsiortou P.[1], Alexopoulos H.[1], Akrivou S.[1], Barba C.[1], Kosmidis M.[1] Dalakas MC. [1,2]

1Neuroimmunology Unit, Department of Pathophysiology, Faculty of Medicine, National and Kapodistrian University of Athens; 2Department of Neurology, Thomas Jefferson University, Philadelphia, USA

poptsiortou@gmail.com

Aims: To study clinicopathological parameters in a 3-generation family with high-titer anti-glutamic acid decarboxylase (GAD) antibodies. High-titer anti-GAD autoantibodies are a hallmark of neurological syndromes including Stiff Person Syndrome (SPS) and autoimmune epilepsy. Low-GAD titers are typically seen in type 1 Diabetes (DM1)

Methods: Sera from three family members were serially tested using ELISA, immunohistochemistry (IHC) on mouse brain sections, primary hippocampal neurons and LIPS (Luciferase Immunoprecipitation Assay). Patients were examined and their medical histories assessed.

Results: All patients had high-titer anti-GAD antibodies (>20,000 IU/ml-ELISA). The index patient, a 25-year-old woman, presented in 2012 with autoimmune epilepsy treated successfully with steroids and levetiracetam. Her serum immunoreacted to hippocampal neurons and brain sections. By 2017, she developed typical SPS, without DM1, with persistently high anti-GAD antibodies (2,5-4,6 x 106 IU/ml) and no significant differences in the immunoreactive pattern. Her father and paternal grandmother have DM1 with high-GAD titers (1,8 x 106 and 0,7 x 106 IU/ml respectively) never observed in DM1 patients alone without neurological manifestations, up to a-5-year follow-up. Their sera did not immunostain hippocampal neurons but bound to cerebellum, similarly to the index case. LIPS revealed a slightly different antigen pattern in all three patients.

Conclusions: This is the first family with very high anti-GAD titers in 3 generations. Whereas the index patient presented with autoimmune epilepsy that evolved into SPS without DM1, her family members had only DM1 and very high anti-GAD antibodies without neurological disease. Whether there is a possible genetic link, remains to be determined.

P027

SOME KYNURENIC ACID ANALOGUES AND THEIR EFFECTS ON A MONOSYNAPTIC TRANSMISSION IN THE HIPPOCAMPUS – STUDIES IN PHYSIOLOGICAL AND ISCHEMIC CIRCUMSTANCES

Evelin Fehér[1,5], Tamás Dudás[5], Anna Zalatnai[5], Tamás Farkas[5], István Szatmári[3], Ferenc Fülöp[3,5], László Vécsei[1,2] and József Toldi[5]

1Department of Neurology, Interdisciplinary Excellence Centre, Faculty of Medicine University of Szeged;
2MTA-SZTE Neuroscience Research Group, Szeged, Hungary ;
3Institute of Pharmaceutical Chemistry, Interdisciplinary Excellence Centre, Faculty of Pharmacy, University of Szeged;
4MTA-SZTE Stereochemistry Research Group;
5Department of Physiology, Anatomy and Neuroscience, Faculty of Science and Informatics, University of Szeged

feher.evelin23@gmail.com

Excitotoxicity is the hallmark of brain ischemia and several neurodegenerative processes, where a tryptophan metabolite kynurenic acid (KYNA), the only-known endogen excitatory amino acid receptor antagonist, can act as a neuroprotective agent. However, the neuroprotective potential of KYNA is limited because it hardly crosses the blood-brain barrier (BBB). This is why BBB-penetrant KYNA derivatives became into the focus of research. Working on this problem, our research group has developed several neuroactive KYNA derivatives during the past fifteen years.

In this study, an evaluation of some new putative neuroprotective derivatives with divergent molecular characters is presented, together with their most typical effects on a monosynaptic transmission in the CA1 region of the hippocampus of rat.

Their effects on the basic neuronal activity (on the field excitatory postsynaptic potentials: fEPSP) were studied using in vitro hippocampal slices in physiological and ischemic circumstances (oxygen glucose deprivation, OGD), respectively.

KYNA and its some derivatives (SZR-72, SZR-105) in 200 μM concentration proved to be inhibitory, while other derivatives (SZR-73, SZR-104) with the same concentration had the opposite effect on fEPSPs. Derivatives with facilitatory effects (in 200 μM) were able to delay significantly the total loss of synaptic transmission in ischemic circumstances.

The possible relations between molecular structures and their physiological effects are discussed.

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P028

EVALUATION OF BLOOD LYMPHOCYTE SUBSETS AND MONOCYTE FUNCTION IN ALZHEIMER'S DISEASE

Andjelka M. Isakovic[1], Maja Jovanovic [1], Elka Stefanova[2], Ljubisa Rakic[3], Marija Jeremic[1], Millica Vukojevic[1], Sonja Misirlic-Dencic[1], Vladimir Kostić[2] and Ivanka Marković[1]

1Institute of Medical and Clinical Biochemistry, Faculty of Medicine, University of Belgrade, Serbia;
2Institute of Neurology, Clinical Center of Serbia, Faculty of Medicine, Belgrade, Serbia;
3Serbian Academy of Sciences and Arts, Belgrade, Serbia

andjelka.isakovic@med.bg.ac.rs

The aim of our study was to assess the blood lymphocyte subsets (T-, B-, NK, NKT cells) in Alzheimer's disease (AD) patients, as well as amyloid beta1-42 (Aβ1-42) phagocytosis by peripheral blood mononuclear cells (PBMCs) isolated from AD patients' peripheral blood.

The patients selected were the ones with probable AD, according to NIA-AA criteria. Control subjects were age- and sex-matched and cognitively unimpaired. Immunophenotypization and Aβ1-42 phagocytosis were determined using flow-cytometry.

The flow cytometric analysis of PBMCs showed the difference in expression of NKT cells (CD3+, CD16, 56+) between AD patients and control subjects ($p=0.001$), but not in expression of B lymphocytes, T-helper, T-cytotoxic lymphocytes or NK cells. PMBCs cultivated with FITC-labelled Aβ1-42 (24 h) showed that percentage of monocytes containing phagocytosed Aβ1-42-FITC was significantly lower in the cells from AD patients compared to the Aβ1-42 uptake by monocytes from the control subjects ($p<0.01$). In addition, flow-cytometric analysis od monocytes' apoptosis markers (Annexin V-FITC/propidium iodide) after 24 hours in culture showed increase in the percentage of monocytes undergoing early (Ann+/PI-) and, particularly, late apoptosis (Ann+/PI+) between AD monocytes, and monocytes derived from control subjects.

These results show the changes in NKT cells and functional properties of the AD patients' monocytes, implicating that further investigation of PBMC and their function may contribute to elucidation of the role of immune cells in AD pathogenesis.

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P029

HISTOPATHOLOGY AND RADIOLOGY OF THE NEURAL RETINA AND OPTIC NERVE IN NONSYNDROMIC CONGENITAL RETINAL NON-ATTACHMENT (NCRNA)

Fatemeh Sadat Rashidi[1], Ehsan Ahmadipour[1], Fahimeh Asadi Amoli[2], Amir Hosein Falahian[3], Hamideh Gholamhoseini[4], Mohamad Ismail Zibaii[5], Nader Maghsoudi[1], Alireza Zali[6], Mostafa Soltan Sanjari[7], Reza Ahadi[5], Noor Mohamad Ghiasvand[6,9]

1Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran;
2Farabi Eye Research Center, Tehran University of Medical Science, Tehran, Iran;
3Department(s) of Radiology, Kansas City Veterans Medical Center, Kansas city, MO 64128, USA;
4Radiology Department, Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran;
5Laser and Plasma Research Institute, Shahid Beheshti University, Tehran, Iran;
6Functional Neurosurgery Research Center, Shohada Tajrish Neurosurgical Center of Excellence, Shahid Beheshti University of Medical Sciences, Tehran, Iran;
7Department of Ophthalmology, Eye Research Center, Rasoul-Akram Hospital, Iran University of Medical Sciences (IUMS), Tehran, Iran;
8Department of Anatomy, School of Medicine, Iran University of Medical Sciences, Tehran, Iran;
9Department of Biology, Grand Valley State University, Allendale, MI 49401, USA

fatemeh.rashidi8kh@gmail.com

Transient expression of ATOH7 gene in embryonic neural retina is required for the genesis of retinal ganglion cells (RGC), hence for optic nerve (ON) development. Different ATOH7 disease alleles could result in different degrees of optic nerve abnormalities; from optic nerve aplasia (ONA) to a wide spectrum of optic nerve hypoplasia (ONH). We have previously shown that the deletion of a cis controlling element upstream of ATOH7 results in nonsyndromic congenital retinal non-attachment (NCRNA) and congenital blindness with no perception of light.

In this study we investigate the histology of optic pathways in a 16-week NCRNA (ATOH7-/-) fetus and an age-matched ATOH7+/+ fetus as control.

We reported this phenotype as a case of ONA. However, because, in the magnetic resonance images of a NCRNA patient, thin linear structures were present in his orbital cones, and the MR images did not allow us to resolve the components of these structures, we could not rule out the presence of thin atrophic/hypoplastic optic nerves. In this report we describe the histopathological differences between optic pathways in these fetuses.

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P030

THE RELATIONSHIP BETWEEN TOXIC ELEMENTS AND ASD: A META-ANALYSIS STUDY

Fatemeh Sayehmiri[1],*, Aryoobarzan Rahmatian[2], Hamed Jafari Mohammadabadi[3], Mohammad Rafiei[4]

1Student research committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran;
2Assistance Professor, Faculty of medicine, Ilam University of Medical Sciences,Ilam, Iran.;
3 School of Medicine, Shiraz university of medical sciences,Shiraz, Iran;
4Associate Professor of Biostatistics, Department of Biostatistics and Epidemiology, Arak University of Medical Sciences, Arak, Iran

fsayehmiri@yahoo.com

Aim: There is a likelihood of a possible relationship between the concentrations of copper, lead, and mercury and autism. The present review was carried out to determine the relationship between the concentrations of these elements and autism by meta-analysis.

Methods: In this study, searching Scopus, PubMed, and Science Direct databases, 18 articles conducted in different countries from 1982 to 2018 were collected. Studies' heterogeneity was investigated using the I2 index. The data were analyzed using R and STATA software.

Results: In these 18 studies, 1797 patients (981 cases and 816 controls) aged 2 to 16 years were examined. Concentration of the samples (blood, hair, and nails) for both case and control groups were evaluated. There was no significant relationship between copper concentration and autism (SMD (95% CI): 0.02(-1.16, 1.20);I2=97.7%; P=0.972); there was a significant relationship between mercury concentration and autism (SMD (95% CI): 1.96(0.56, 3.35);I2=98.6%; P=0.006); there was also a significant relationship between lead concentration and autism (SMD (95%CI): 2.81(1.64,3.98); I2=97.8%; P=0.000).

Conclusion: There is, nevertheless, a significant relationship between mercury concentration and autism. Thus, the concentration of mercury can be listed as a pathogenic cause (disease-causing) for autism.

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POSTER SESSION 1

P031

EFFICACY OF A SELECTIVE NF-KB INHIBITOR IN RATS' MODELS OF DEPRESSION AND MANIA

Ahmad Nassar[1]; Jacob Kaplanski[1]; Abed N. Azab[1,2]

1Department of Biochemistry and Pharmacology;
2Department of Nursing;
Faculty of Health Sciences, Ben-Gurion University of the Negev;
Beer-Sheva, 84105, Israel

azab@bgu.ac.il

Background: Mental illnesses influence millions of people worldwide causing enormous burden to patients and their families. Despite the availability of numerous psychotropic drugs, many patients do not respond to treatment and suffer chronicity of symptoms. Immune disturbances have been associated with psychiatric illnesses including bipolar disorder. Several studies demonstrated an association between nuclear factor k B (NF-kB) and mental disorders.

Objectives: This study was undertaken to examine the effects of a selective NF-kB inhibitor (JSH-23) on animal models of mania and depression.

Methods: We examined the effects of chronic treatment with JSH-23 in rat models of depression (sucrose consumption test [SCT] and forced swim test [FST]) and mania (amphetamine [AMPH]- induced hyperactivity test). Rats were divided into two groups (n=24 per group): Control group - was treated once daily for 14 days with vehicle (DMSO); JSH-23 group - was treated once daily for 14 days with JSH-23 (3mg/kg) through intraperitoneal injection. Rats were subjected to a SCT at baseline, day 6, and day 14. On day 14, after conduction of the SCT, control and JSH-23-treated rats were divided to two sub-groups (n=12 per group): 1) control - subjected to FST, 2) control - subjected to AMPH test, 3) JSH-23 - subjected to FST, 4) JSH-23 - subjected to AMPH test.

Results and Discussions: Sucrose consumption was significantly higher in JSH-23-treated rats after 6 and 14 days. JSH-23 significantly reduced immobility time and increased swimming time in the FST. On the other hand, JSH-23 did not affect total distance in the AMPH test. These results suggest that JSH-23 exerts antidepressant-like but not antimanic-like effects.

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P032

EFFECTS OF TREATMENT WITH A SELECTIVE NF-KB INHIBITOR ON CLINICAL OUTCOMES AND BRAIN LEVELS OF INFLAMMATORY MEDIATORS IN POST-STROKE RATS

Jacob Kaplanski[1], Raneen Hijaze[1], Ahmad Nassar[1], Matthew Boyko[2], Abed N. Azab[1],[3]

1Department of Biochemistry and Pharmacology;
2Department of Anesthesiology and Critical Care, Soroka University Medical Center;
3Department of Nursing;
Faculty of Health Sciences, Ben-Gurion University of the Negev;
Beer-Sheva, 84105, Israel

moshiko22@bezeqint.net

Background: Few efficacious therapeutic options are available for the treatment of ischemic stroke. One of the key cellular players in the inflammatory process after the occurrence of ischemic stroke is the transcription factor nuclear factor (NF)- k B.

Objectives: This study was examined the effects of a selective NF-k B inhibitor (JSH-23) on clinical outcomes and brain inflammatory markers in post-stroke rats.

Study Outcomes: Clinical measures – mortality, neurological score (NS) and body temperature (BT). Inflammatory markers – Interleukin (IL)-6, prostaglandin (PG) E2 and tumor necrosis factor (TNF)-α in the hypothalamus (HT), hippocampus (HC) and frontal cortex (FC).

Methods: Rats were subjected to a permanent middle cerebral artery occlusion (MCAO). Control animals underwent a sham surgery. Rats were treated once daily with JSH-23 (3 mg/kg) for 3 days. Control animals were treated with vehicle (DMSO). Cumulative 3-days mortality, NS and BT were monitored. Brain samples were homogenized and centrifuged, and supernatants were collected. IL-6, PGE2 and TNF-α levels were determined by ELISA.

Results and Discussions: Cumulative 3-days mortality did not differ significantly between JSH-23-treated and vehicle-treated MCAO rats (10% vs. 25%, respectively, P = 0.184). NS was significantly lower in JSH-23-treated MCAO rats as compared to vehicle-treated MCAO rats at 48 h after surgery (P = 0.008). Overall, JSH-23 treatment did not significantly alter BT in post-MCAO rats. There were no prominent differences in IL-6, PGE2 and TNF-α levels in HT, HC and FC between MCAO and sham-operated rats at 72 h after surgery. Moreover, treatment with JSH-23 did not alter IL-6, PGE2 and TNF-a levels in MCAO rats. These results suggest that sub-chronic treatment with JSH-23 did not markedly influence morbidity and mortality in post-stroke rats.

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P034

EFFECTS OF SCALP-ACUPUNCTURE THERAPY ON ACTIVATION OF NEURAL PROGENITOR CELLS IN NEONATAL HYPOXIA-ISCHEMIA OF RATS

Da Hee Jung, Malk Eun Pak, Hong Ju Lee, Sung Min Ahn, Hwa Kyoung Shin, Byung Tae Choi

Department of Korean Medical Science, Graduate Training Program of Korean Medicine for Healthy-Aging, School of Korean Medicine, Pusan National University, Yangsan 50612, Republic of Korea

jjj262999@pusan.ac.kr

Aims: Electric acupuncture therapy, alternating current stimulation, on the scalp over the motor cortex (EASM) is used for the treatment of brain disorders. We investigated whether EASM could promote functional improvement in a neonatal hypoxia–ischemia (HI) rat model via the enhancement of activating neural stem cells.

Methods: Neonatal HI Sprague–Dawley rats (P7) underwent EASM (2 Hz with 1, 3, and 5 mA) for 20 min from 4–6 weeks after birth. We analyzed behavioral and physiological changes using tests for motor and memory function, immunofluorescence staining, and western blotting.

Results: HI rats with EASM improved motor and memory function, with the greatest improvement after 3 mA EASM. The corpus callosum was significantly thicker and showed a significant increase in proliferating cells and oligodendrocytes in the 3 mA EASM group. We observed proliferating cells, and an increase in newly developed neurons and astrocytes in the subventricular zone and dentate gyrus in the 3 mA EASM group compared with the HI group. Moreover, HI rats showed increased expression of oligodendrocytes and neuron markers in the corpus callosum and hippocampus in the 3 mA EASM group.

Conclusion: These results suggested that EASM treatment promotes functional improvements following neonatal HI assault, via the proliferation and differentiation of neural stem cells. This effect was strongest after 3 mA EASM, suggesting that this is the optimal treatment dose.

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P036

ELECTROACUPUNCTURE AMELIORATES MOTOR DYSFUNCTIONS VIA PROTECTION OF DOPAMINERGIC NEURON INVOLVING BDNF/GDNF SIGNALING IN PARKINSON'S DISEASE MOUSE MODEL

Malk Eun Pak, Da Hee Jung, Hong Ju Lee, Sung Min Ahn, Hwa Kyoung Shin, Byung Tae Choi

Department of Korean Medical Science, Graduate Training Program of Korean Medicine for Healthy-Aging, School of Korean Medicine, Pusan National University, Yangsan 50612, Republic of Korea

cleargirl46@naver.com

Aim: Electroacupuncture (EA) is often used as a complementary therapy for Parkinson's disease (PD) to ameliorate neurological dysfunction. We investigated the effects of EA treatment on behavioral dysfunction, loss of dopaminergic (DA) neuron, and activation of neurotrophic factors in PD animal model.

Methods: EA treatment was delivered via electrical stimulation (2 Hz, 1 mA) at two acupoints, Baihui (GV20) and Dazhui (GV14) in MPTP-induced PD mouse model and examined behavioral, histological and molecular changes by using behavior tests related to motor function, immunofluorescence staining, western blot and ELISA analysis.

Results: Behavioral tests showed that EA treatment alleviated motor dysfunction caused by MPTP on rotarod and cat-walk test. MPTP caused a significant loss of DA neuron by cell death in the striatum and substantia nigra, but EA treatment significantly restored DA neuron in these regions. EA treatment induced upregulation of brain-derived neurotrophic factor (BDNF) and glia cell line-derived neurotrophic factor (GDNF) in midbrain with increased expression of its receptors, tropomyosin receptor kinase B and GDNF family receptor alpha-1. Furthermore, EA treatment induced upregulated Akt, cAMP response element binding protein (CREB) and Pitx3 expression.

Conclusion: Our results demonstrate that EA treatment may protect DA neuron via upregulation of BDNF/GDNF signaling related Akt/CREB/Pitx3, which subsequently improves motor function. Therefore, EA treatment offers adjuvant therapy for PD patient to recover motor dysfunction.

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P037

MRI CONTRAST AGENTS: EVIDENCE OF GADOLINIUM METAL DEPOSITION IN THE SPINAL CORD AND PERIPHERAL NERVES

Safia Alkhunizi[1], Wassim Abou-Kheir[1] and Nada Lawand[1,2]

1Department of Anatomy, Cell Biology and Physiological Sciences, Faculty of Medicine, American University of Beirut, Beirut, Lebanon; 2Department of Neurology, Faculty of Medicine, American University of Beirut, Beirut, Lebanon

sma77@mail.aub.edu

Aims: Gadolinium-Based Contrast Agents (GBCAs) are used worldwide to enhance the quality of MRI scans. Recent postmortem studies have shown that GBCAs administration result in Gadolinium (Gd) metal deposition in the brain and other organs. The aim of this study is to investigate if repeated exposure to linear and macrocyclic-GBCAs leads to Gd deposits in the spinal cord and peripheral nerves.

Methods: Sprague-Dawley rats were given daily injections of two types of GBCAs, Gadodiamide and Gadoterate-meglumine for a period of 20 days. Two different doses of both substances were used: 2.5 mmol/kg and 0.6 mmol/kg. The control group received saline injections. Rats were scarified and the spinal cord, brain, and peripheral nerves (sciatic and trigeminal) were extracted. Inductively Coupled-Plasma Mass-Spectrometry (ICP-MS) was used to quantify Gd in the samples.

Results: The average total [Gd] detected for Gadodiamide and Gadoterate-meglumine, respectively, were: 47.6 ± 6.74 and 5.02 ± 0.59 nmol/g in the spinal cord, and 103 ± 6.48 and 1.04 ± 0.07 nmol/g in peripheral nerves for the high dose, and 14.15 ± 3.10 nmol/g and 2.03 ± 0.48 nmol/g in the spinal cord for the low dosage groups. This was significantly higher than the controls. Both agents also resulted in significantly high deposits in the cerebrum, brainstem and cerebellum regions.

Conclusions: This study provided the first evidence for Gd-deposition in the spinal cord and peripheral nerves. The safety of GBCAs and the effect of such metal deposition on sensory and motor neuronal functions should be further evaluated.

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P038

BEHAVIORAL IMPAIRMENT AND DECREASED HIPPOCAMPAL NEUROPLASTICITY IN ANIMAL MODEL OF INHALANT ABUSE

Hanaa Malloul[1,2,3], Sara Bonzano[2,3], Mohammed Bennis[1], Giovanna Gambarotta[4], Silvia De Marchis[2,3] and Saadia Ba-M'hamed[1]

1Laboratory of Pharmacology, Neurobiology and Behavior (URAC-37), University Cadi Ayyad, Faculty of Sciences Semlalia, Marrakech, Morocco;
2Department of Life Sciences and Systems Biology, University of Turin, Via Accademia Albertina 13, 10123 Torino, Italy;
3Neuroscience Institute Cavalieri Ottolenghi (NICO), Orbassano, Italy;
4Department of Clinical and Biological Sciences, University of Turin, Orbassano, Italy

hanaamalloul@gmail.com; silvia.demarchis@unito.it; bamhamed@uca.ma

Aims: Thinner is a volatile solvent widely used in various industrial applications and it is a subject to abuse by inhalation for their psychoactive properties. Despite the prevalence of inhalant abuse, the addictive potential and the mechanisms underlying the effects of inhalants abuse on the brain are far to be fully understood. In this study, we investigate the consequences of thinner inhalation at behavioral and structural/molecular levels in adult mice.

Methods: Rewarding effects, depression-related responses, anxiety, learning and memory functions were assessed in adult mice following acute, subchronic and chronic exposure to thinner vapor. Next, given the well-known implication of adult hippocampal neurogenesis in disease conditions associated with drug abuse, we characterized its alteration following thinner treatments. Finally, we measured changes in the hippocampus at the molecular level by analyzing the expression of the plasticity-related genes.

Results: We found that prolonged, but not acute thinner exposure, induces a positive conditioned place preference to inhaled thinner. Moreover, both subchronic and chronic treatments led to anxiolytic and depression-like behaviors with altered learning and memory functions. Notably, prolonged thinner inhalation strongly affected adult neurogenesis in the dentate gyrus by reducing progenitor cell proliferation and impairing the survival of newborn neurons. Furthermore, a down-regulation in the expression of BDNF and NMDA receptor subunits as well as a reduction in CREB expression/phosphorylation were found in the hippocampi of chronically treated mice.

Conclusions: Our findings demonstrate drastic hippocampal molecular/structural changes that are likely to be directly involved in the behavioral dysfunctions associated to inhalant abuse.

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P039

DYSREGULATION OF THE BRAIN PYRUVATE DEHYDROGENASE IN AN ANIMAL MODEL OF COEXISTENCE OF DEPRESSION AND HYPOTHYROIDSM

Głombik K, Detka J, Kurek A, Budziszewska B.

Department of Experimental Neuroendocrinology, Institute of Pharmacology, Polish Academy of Sciences, Cracow, Poland

glombik@if-pan.krakow.pl

Aims: The relationship between thyroid dysfunction and mood disorders has been observed clinically for a long time but the effect of thyroid hormones on processes in the brain after the developmental period is still poorly known. Recent clinical studies have provided evidence for involvement of thyroid hormones in brain metabolic disturbances observed in depression. Our goal was to investigate selected metabolic markers, including pyruvate dehydrogenase (PDH), a key metabolic enzyme complex, in the frontal cortex in an animal model of co-occurrence of depression and hypothyroidism.

Methods: Study was performed in an animal model of depression (Wistar-Kyoto rats) and model of coexistent depression and hypothyroidism (Wistar-Kyoto rats treated with 6-n-propyl-2-thiouracil - PTU). PTU (0.05 %) was administered in drinking water for 3 weeks. Enzyme-linked immunosorbent, colorimetric assays and Western blot were applied to examine the metabolic changes in the frontal cortex.

Results: The applied model was verified behaviorally nad hormonally. We demonstrated a decrease in the level and activity of PDH and reduced expression of pyruvate dehydrogenase kinase 4 (PDK4) in the frontal cortex in rat model of coexistent depression and hypothyroidism. Additionally, we showed diminished level of pyruvate and changes in the levels of mitochondrial respiratory complexes in used model.

Conclusions: In summary, our study demonstrated that in the model of coexistent depression and hypothyroidism dysregulation of the proper action of PDH, which combines the Krebs cycle and oxidative phosphorylation to the glycolysis, gluconeogenesis and lipid metabolism pathways, is observed.

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P040

OREXIN-A CHANGES IN BRAIN OF THE EARLY-LIFE STRESSED ADULT RATS TREATED WITH ESCITALOPRAM OR VENLAFAXINE – AN IMMUNOHISTOCHEMICAL STUDY

Miłosz Gołyszny, Tomasz Ludyga, Łukasz Filipczyk, Artur Pałasz, Ewa Obuchowicz

Medical University of Silesia, Katowice, Poland

miloszgolyszny@o2.pl

Aims: The study was carried out to estimate OX-A expression in the lateral hypothalamus of rats subjected to maternal separation and escitalopram or venlafaxine.

Material and Methods: Maternal separation was used as a model of depression. Pups of Wistar rats were maternally separated from postnatal day 2-15 for 6h per day (between 9 a.m. and 3 p.m.). In the adulthood (2,5 months) male stressed or control rats were assigned to saline, escitalopram or venlafaxine group. Drugs (10mg/kg ip.) or saline were administrated once daily for 21 days. In the last 3 days, behavioral tests (forced swimming test, elevated plus-maze test) were performed. The blood samples and dissected brains were collected 24 hours after the last dose of the drug. The OX-A immunopositive cells have been visualized using immunohistochemical staining.

Results: In the hypothalamus of the stressed rats and in the non-stressed rats treated with escitalopram expression of OX-A was increased. We observed also alterations in OX-A immunopositive cells in stressed treated with escitalopram or venlafaxine groups.

Conclusions Maternal sepatation causes an increase of the OX-A expression in the lateral hypothalamus, what is confirmed role of the orexinergic transmission in stress-related behaviors. The antidepressant drugs give various acts in naive and separated rats.

P041

INVESTIGATING WHOLE-BRAIN MRI MARKERS IN NEUROPSYCHIATRIC DISORDERS – EMERGING DIMENSIONS IN MORPHOMETRIC SPACE

João Valente Duarte[1,2,3], Nuno Madeira[4,5], Ricardo Martins[1,2,3], Gabriel Nascimento Costa[1,2,3], António Macedo[4,5], Miguel Castelo-Branco[1,2,3]

1Coimbra Institute for Biomedical Imaging and Translational Research (CIBIT), University of Coimbra, Portugal;
2Institute of Nuclear Sciences Applied to Health (ICNAS), University of Coimbra, Portugal;
3Institute for Biomedical Imaging and Life Sciences (CNC.IBILI), Faculty of Medicine, University of Coimbra, Portugal;
4Department of Psychiatry, Centro Hospitalar e Universitário de Coimbra, Portugal;
5Institute of Psychological Medicine, Faculty of Medicine, University of Coimbra, Portugal

joaovduarte@gmail.com

Aims: Schizophrenia is believed to be a neurodevelopmental disease with high heritability. While established markers like cortical thickness and grey matter volume are heavily influenced by post-onset changes and thus provide limited possibility of accessing early pathologies, gyrification is assumed to be more specifically determined by genetic and early developmental factors. The aim of the study is to compare different morphometric features in psychiatric disorders.

Methods: We included in this study 20 schizophrenia patients, 20 bipolar disorder patients and 20 age- and sex-matched healthy controls. We performed statistical analyses with CAT12/SPM12 applying general linear models for four morphometric measures: gyrification and cortical thickness (surface based morphometry), and whole brain GM/GM volume (VBM). We tested group effect using age and gender as covariates (and total intracranial volume for VBM).

Results: VBM analysis revealed a SCZ vs. CNT group effect on regional GM volume ($p<0.05$; FWE correction) in the right globus pallidus. There was no group effect on WM volume when correcting for multiple comparisons, although we observed differences near the superior frontal gyrus (BA9/10) and superior temporal gyrus (BA38), neither on cortical thickness. Interestingly, gyrification was altered between clinical groups (BPD vs. SCZ) in supramarginal gyrus (BA40) and inferior frontal gyrus (BA47), although at uncorrected $p<0.001$.

Conclusions: A conjunction analysis of different morphometric features might help to elucidate distinct phenotypes in psychiatric disorders. Morphological alterations with different etiologies can serve as neuroimaging-derived biomarkers that can discriminate schizophrenia from bipolar disease. Further investigation is warranted to relate these changes with clinical phenotype.

Funding: This research work was funded by the Portuguese Foundation for Science and Technology (FCT) (grants: COMPETE UID/NEU/04539/2013, SAICTPAC/0010/2015, BIGDATIMAGE-CENTRO-01-0145-FEDER-000016, FCT/COMPETE 2020, QREN CENTRO-07-ST24-FEDER-00205).

P042

GENERATION OF AN IN VITRO MODEL OF PARKINSON'S DISEASE TO EXPLORE THE NEUROPROTECTIVE EFFECTS OF MESENCHYMAL STEM CELLS SECRETOME

Ana Marote[1,2,3], Bárbara Mendes-Pinheiro[1,2], Eduardo Gomes[1,2], Nuno J. Lamas[1,2], Luísa Pinto[1,23], Laurent Roybon[4], António J. Salgado[1,2]

1Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal;
2ICVS/3B's, PT Government Associate Laboratory, Braga/Guimarães, Portugal;
3Behavioral and Molecular Lab (Bn'ML), University of Minho, Braga Portugal;
4Stem Cell Laboratory for CNS Disease Modeling, Wallenberg Neuroscience Center, Department of Experimental Medical Science, BMC A10, Lund University, Lund, Sweden

anammarote@gmail.com

Aims: Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons from the substantia nigra pars compacta leading to the denervation of the nigrostriatal tract, and a significant reduction of dopamine at the striatal level. In our study, we attempted to model these biochemical dysfunctions, by exposing pluripotent stem cell derived dopaminergic neurons to 6-OHDA. Based on previous data from our group showing the therapeutic potential of mesenchymal stem cells (MSCs) secretome in an animal model of PD, we also aimed to use our established in vitro model to provide a mechanistic insight on the neuroprotective effects of MSCs secretome.

Methods: For that, we have established an embryoid body-based dopaminergic differentiation protocol and provided a collagen matrix to promote neurite outgrowth and render a platform to induce 6-OHDA mediated toxicity. Subsequently, we have assessed cell viability, dopaminergic neurons' morphology and reactive oxygen species production as readouts of 6-OHDA induced toxicity and MSCs secretome neuroprotective effects.

Results: Using our model, we were able to induce significant morphological alterations in the neurite arborization of 6-OHDA exposed dopaminergic neurons, which were partially reverted by incubation with MSCs secretome.

Conclusions: This model can be used as a simple and affordable tool to investigate the use of new therapeutic tools for PD, such as MSCs secretome.

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P043

NOVEL EXOSC3 PATHOGENIC VARIANT RESULTS IN A MILD COURSE OF NEUROLOGIC DISEASE WITH CEREBELLUM INVOLVEMENT

Maria Catalina Craciun[1],[3], Octavian Geamanu[2], Diana Le Duc[3]

1Division of Physiology and Neuroscience, "Carol Davila" University of of Medicine and Pharmacy, Bucharest, Romania;
2 "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania;
3Institute for Human Genetics, University Clinics Leipzig, Leipzig, Germany

catalina.craciun10@gmail.com

Aims: EXOSC3-related autosomal recessive neurodevelopmental disorders are rare entities with variable clinical course and prognosis. They are characterized by hypoplasia of cerebellar structures and pons, degeneration of the anterior horn cells, and motor as well as neurocognitive impairment. Phenotypic expression is variable with an overall poor outcome.

Methods: Current research suggests clear genotype-phenotype correlations among EXOSC3-pathogenic-variants carriers. Homozygosity for the EXOSC3 variant c.395A > C, p.(Asp132Ala) is proposed to lead to a rather mild phenotype compared to compound-heterozygous EXOSC3-pathogenic-variants carriers with lethal neurological disease in very early childhood. We tested the patients included in the study by clinical exome sequencing (Trusight One Illumina).

Results: In this study, we report two siblings (21- and 8-year-old) affected by pontocerebellar hypoplasia type 1B (PCH1B) with an unusual presentation. We identified compound heterozygosity for the well-established EXOSC3 variant c.395A > C, p.(Asp132Ala) and the novel variant c.572G > A, p.(Gly191Asp), expanding the genetic spectrum. Phenotypic presentation of the siblings was strikingly different from that of literature reports with a surprisingly mild disease manifestation and an unexpected intrafamilial variability.

Conclusion: This study demonstrates the extensive clinical heterogeneity and the broad phenotypic spectrum associated with EXOSC3-associated disorders. Enlargement of sample sizes and reports of novel cases will be essential for the delineation of associated phenotypes.

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P044

DIRECT IN VIVO REPROGRAMMING TECHNOLOGY AIMED TO RESTORE CELULAR BALANCE IN THE AGED BRAIN POST STROKE

Gresita Andrei[1], Dumbrava Danut-Adrian[1], Popescu-Driga Mircea[1], Surugiu Roxana[1], Popa-Wagner Aurel[1,2,3]

1University of Medicine and Pharmacy Craiova, Neurobiology of Aging Group, Craiova, Romania;
2Department of Neurology, Chair of Vascular Neurology and Dementia, University of Medicine Essen, Germany;
3Department of Neurology, Chair of Vascular Neurology and Dementia, University of Medicine Essen, Germany

aurel.popa-wagner@geriatrics-healthyageing.com; gresitaandrei@gmail.com

Ischemic stroke represents the 2nd leading cause of death worldwide and the primary reason for sustained disability for which no cure exists. Post stroke, neurons are frequently lost in the infarct core. On the other hand, other cells such as astrocytes become reactive and proliferative, disrupting the neuronal vs non-neuronal cell balance in the lesioned area, especially in the aged brain. Therefore, restoring the ballance between neurons and non-neuronal cells within the post-stroke perilesional area is crucial for post-stroke recovery. In addition to this, proliferating glia become reactive and build up gliotic scars that are initially protective by confining the damaged area.

In the long-term, however, the gliotic scar is deleterious by acting as a barrrier to neural regeneration. “Melting” glial scars has been attempted for decades with little success. Alternative strategies include transforming inhibitory gliotic tissue into an environment conducive to neuronal regeneration and axonal growth. The latter idea has gained momentum following the discovery that in vivo direct lineage reprogramming in the adult mammalian brain is a feasible strategy for reprogramming non-neuronal cells into neurons; this exciting new technnology emerged as a new approach to circumvent cell transplantation.

However, the potential of this new methodology has not been tested to improve restoration of structure and function in the hostile environment caused by the fulminant inflammatory reaction in the brains of aged animals following stroke. To this end, used retroviral/lentiviral delivery systems encoding transcription factors, SOX2 or NeuroD1 or two transcription factors (Neurog2 and Bcl-2) to target astrocytes in the neocortex of aged rats.

Successful direct in vivo reprogramming of reactive glia into neuroblasts and mature neurons has been assessed by cellular phenotyping. Since there is no restorative treatment available for stroke, and given the overwhelming importance of stroke therapy for both patients and society, this approach, could be a breakthrough in the field.

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P045

DETECTION OF REDUCED INTERHEMISPHERIC COMMUNICATION BETWEEN PRIMARY MOTOR CORTICES IN CEREBELLAR KAINIC ACID INDUCED DYSTONIA

Alexandru Țîrlea[1], Elena Laura Georgescu[1], Ioana Antoaneta Georgescu[1], Denise C.M. Zahiu[1], Alexandru Șteopoaie[1], Adrian Pană[1], Adriana Monica Nichita[1], Sebastien Vanhaeren[1], Mădălina Popescu[1], Ana-Maria Zăgrean[1], Daniela Popa[1,2]

1Division of Physiology and Fundamental Neuroscience, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania;
2Institut de Biologie de l'Ecole Normale Supérieure, INSERM U1024, CNRS UMR8197, Paris, France

stefan.tirlea@stud.umfcd.ro

The primary motor cortices play the most important role in generating movement related neural impulses and control the execution of voluntary muscular activity, together with the cerebellum and basal ganglia. The synchronization of neural activity in the cerebello-cortical network is crucial for the regulation of complex movements, even though some aspects of the cerebellar contribution to oscillatory brain activity remain still unclear. The aim of this research is to study the interhemispheric cortical communication between the motor cortices during dystonia, which is a neurological movement disorder syndrome consisting in sustained or repetitive involuntary muscle contractions.

We pharmacologically induced dystonia to adult male albino mice by administering low doses of kainic acid on the left cerebellar hemisphere and investigated using electrocorticography the coherence between the right and left motor cortices, before and during dystonia, for 5 consecutive days.

The results showed a progressive coherence decrease in all frequency bands during the first three days, followed by an increase in low-gamma and high-gamma bands in day 5 of kainic acid administration.

In conclusion, cerebellar dysfunction during dystonia causes a loss of connectivity in the motor cortices, which may block propagation of abnormal oscillations, thus showing evidence of apparent cortical compensation to the initial disturbances.

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P046

ECOG AND EMG CONNECTIVITY DURING CEREBELLAR KAINIC ACID-INDUCED DYSTONIA IN MICE

Carmen-Denise-Mihaela Zahiu[1], Elena-Laura Georgescu[1], Ioana Georgescu[1], Alexandru Steopoaie[1], Adrian Pana[1], Alexandru Tarlea[1], Daniela Popa[1,2] and Ana Maria Zagrean[1]

1Division of Physiology and Fundamental Neuroscience, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; 2UMR8197 Institut de biologie de l'Ecole Normale Supérieure (IBENS), Paris, France

carmen.zahiu@umfcd.ro

The aim of this study was to investigate the relationship between motor cortex oscillation and neck muscles activity, assessed by electrocorticogram (ECoG) - electromyogram (EMG) coherence, during dystonic attacks in a mouse model of dystonia.

Methods: We used a kainic-induced dystonia model by performing repeated microinjections of low doses of kainic acid into the left cerebellar cortex, for five consecutive days. Motor cortices ECoG and neck muscles EMG were recorded in freely moving mice, before and during the dystonic behavior in order to analyse them in Matlab for power spectral densities and coherence.

Results: Cerebellar kainic acid microinjection generated reproducible dystonic motor behavior, affecting the muscles located ipsilateral to the injection site. The right motor cortex and left neck muscles coherence increased in beta, theta and gamma band whereas the left motor cortex and right neck muscles coherence decreased in the delta, theta, beta and low gamma band after cerebellar kainate injection.

Conclusions: We observed an abnormal drive to dystonic muscles after kainate injection in cerebellum. Our results are consistent with Grosse P. (2004) and Cisotto G. (2017) clinical studies in focal and limbs dystonia. Further investigation needs to be performed to have new insight in the physiopathology of dystonia.

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P047

OLFACTORY BULBECTOMY INDUCES MICROGLIOSIS AND INCREASED LEVELS OF CHOLINE ACETYLTRANSFERASE AND NERVE GROWTH FACTOR IN MOUSE HIPPOCAMPUS

O. Nedogreeva, M. Stepanichev, N. Gulyaeva

Institute of Higher Nervous Activity and Neurophysiology of RAS, Moscow, Russia

nedogreewaolga@gmail.com

Hippocampus (HC) receives input from the basal forebrain cholinergic nuclei (BFCN): the medial septal nucleus (MS) and diagonal band of Broca nuclei (DBB), which are in turn sensitive to the hippocampal nerve growth factor (NGF) input. Olfactory bulbectomy (OB) in rodents causes significant cognitive impairments and cholinergic hypofunction in BFCN; therefore, it is a widely used model for some features of depression and neurodegeneration. To assess if the impairments caused by OB are accompanied by changes in both inputs and microglia state we examined the expression of choline acetyltransferase (ChAT) and NGF in HC and MS and counted microglial cell in different HC regions of olfactory bulbectomized (OBX) mice 30 days after surgery.

Male C57Bl/6 mice were bulbectomized by aspiration. The sham-operated animals were used as a control group. Brain tissue was sampled thirty days after surgery and used for immunohistochemistry (microglial expression of Iba1) and Western-blot (ChAT and NGF) analysis.

In the MS, the ChAT and NGF levels remained unchanged. The content of ChAT in the hippocampus was two times higher and the NGF level was increased by 90% (both $p < 0.05$) after OB as compared to the sham group. The number of microglial cells was significantly increased by two-fold in polymorphic layer of the DG ($p < 0.01$) and by 28% in CA1 stratum oriens ($p < 0.05$).

Our data suggest that OB leads to gliosis in HC and elevated ChAT and NGF rates in HC but not in MS.

Supported by RAS according to FIMT project.

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P049

DIFFERENCES AND SIMILARITIES IN MOLECULAR SIGNATURE OF DEPRESSION AND PTSD

Miroslav Adzic[1] and Danka Savic[2]

1Department of Molecular Biology and Endocrinology, VINCA Institute of Nuclear Sciences, University of Belgrade, Belgrade, Serbia.;
2Laboratory of Theoretical and Condensed Matter Physics, VINCA Institute of Nuclear Sciences, University of Belgrade, Belgrade, Serbia.

miraz@vinca.rs

Aims: Comorbidity between post-traumatic stress disorder (PTSD) and major depressive disorder is common. The purpose of this study was to identify genes and pathways associated with PTSD and depressive symptoms in order to better define each of the diagnoses.

Methods: 263 male subjects were categorized in four groups: A) current PTSD (n = 68), B) lifetime PTSD (n = 42), C) trauma controls (n = 74), and D) healthy controls (n = 79). Clinical assessment included PTSD and depressive symptoms. We examined expression profiles of genes involved in several processes known to be altered in psychiatric diseases: G-protein signaling (GNAS, GNAI, RGS2, ARRB1, ARRB2), immune response (CD8α, CD8β, IL1β, IL6, IL8, MAPK14, IDO1, P2X7), stress response (NR3C1, NR3C2, MAPK8), monoamine signaling (S100A10, SLC6A4, SLC18A2), metabolism (ADA, DPP4, TSPO, PREP), cell growth/proliferation (MAPK1, MAPK3, DUSP1, CREB1, CREB2) and cell death (ODC1) signaling in the peripheral blood mononuclear cells of the subjects. Structural equation modeling (SEM) was used to determine the associations of gene expression profiles with depressive or PTSD symptoms.

Results: The model that included all mRNAs and symptom scores revealed that ARRB2, TSPO, NR3C1 and NR3C2 were significantly associated with depression symptoms, while NR3C1, ARRB1, ARRB2 and MAPK14 were significantly associated with PTSD symptoms.

Conclusion: Our results emphasize that stress and G-protein signaling associate with both disease symptoms and that different genes are specifically related to depression and PTSD. In addition, PTSD symptoms are more related with alterations in proliferative and inflammatory processes.

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P050

RESULTS OF CLINICAL EXOME ANALYSIS IN RARE NEURODEGENERATIVE DISORDERS IN SERBIAN POPULATION

Marija Brankovic[1,2], Valerija Dobričić[1,2] , Aleš Maver[3], Gaber Bergant[3] , Marina Svetel[1,2] , Igor Petrović[1,2] , Stojan Perić[1,2] , Milena Janković[1,2], Ana Marjanovic[1,2], Elka Stefanova [1,2] , Ivana Novakovic[1,2], Borut Peterlin[3] and Vladimir Kostic[1,2]

1Neurology Clinic, Clinical Center of Serbia, Belgrade, Serbia;
2School of Medicine, University of Belgrade, Belgrade, Serbia;
3Clinical Institute of Medical Genetics, University Medical Centre Ljubljana, Ljubljana, Slovenia

mara.brankovic@gmail.com

Aims: The aim of the study was to analyze the genetic bases of a wide range of neurodegenerative disorders manifesting in motor and cognitive impairments using next generation of sequencing (NGS) diagnostic panel.

Material and Methods: Study included 26 unrelated and 3 siblings pair patients diagnosed with various neurodegenerative diseases, all negative after targeted genetic testing. Preference was given to family cases with early presentation or complex phenotype (suggesting genetic heterogeneity). Clinical exome sequencing (CES) panel for 4813 genes with known associated clinical phenotypes was performed using TruSight One Panel on Illumina MiSeq NGS platform. Variants discovery was performed according to Genome Analysis Toolkit (GATK) workflow. Variants were stored and annotated in the variant collection and annotation system, based on vtools and ANNOVAR software. The strategy for data interpretation was primarily based on the combined disease and phenotype gene target approach. For pathogenic variants confirmation by Sanger sequencing was done.

Results: We revealed 8 missense and 1 splice pathogenic variants in 7 different genes related to rare neurodegenerative disorders in 7 patients. Pathogenic variants in *TUBB4A*, *PANK2*, *SETX*, *MFSD8* and *PSEN1* genes have been compatible with the clinical phenotype of the patients. Furthermore, variants in *DCTN1* and *PDGFRB* genes have been detected as possible cause of disease in two cases. In the rest of cases genetic diagnosis remains unclear.

Conclusion: These results signify the role of CES in diagnosis of undetermined cases of neurodegenerative diseases and gave us insight in complexity of genetics of this group of disorders.

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P051

METFORMIN EXACERBATES MYELIN DAMAGE IN HIGH FAT DIET-FED C57BL/6J MICE

Darko Ciric[1], Tamara Martinovic[1], Sasa Petricevic[2], Vladimir Trajkovic[3], Vladimir Bumbasirevic[1], Tamara Kravic-Stevovic[1]

1Institute of Histology and Embryology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia;
2Faculty of Pharmacy, Novi Sad, Serbia;
3Institute of Microbiology and Immunology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

darkociric@gmail.com

Aims: The aim of this study was to assess the effects of metformin on sciatic nerve damage in high fat diet (HFD) mouse model of metabolic syndrome and type 2 diabetes.

Methods: Control group of male C57BL/6J mice was fed with a standard chow and the other two groups of male C57BL/6J mice with a HFD for 6 months. Metformin was given orally to mice fed with HFD during the last month. For transmission electron microscopy samples were fixed in glutaraldehyde, post-fixed in osmium tetroxide and embedded in Epoxy resins. Ultrathin sections were examined on transmission electron microscope (TEM).

Results: Electron microscopic analysis of sciatic nerves in control group showed that the majority of axons were without signs of alteration. In HFD groups alterations were more frequently present, as a wide separations of myelin lamellae in the central parts of the myelin sheet or as a wide axon myelin separations at the interface of Schwann cells and the axoplasm. Mice fed with HFD had higher numbers of altered myelinated axons than control animals ($P<0.05$). Metformin treatment aggravated the nerve damage. The differences between metformin-treated HFD mice and both control and HFD mice in the number of damaged fibers were highly statistically significant ($P<0.01$). Nerve fibers myelination was analyzed using g-ratio calculation and showed no statistically significant difference between different groups.

Conclusions: Results of our study on the effects of metformin indicates caution when deciding about optimal treatment modalities in in patients developing diabetic neuropathy.

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P052

WRITING KINEMATICS IN PEDIATRIC ONSET MULTIPLE SCLEROSIS

Nikola Ivančević[1], Marija Novičić[2], Vera Miler-Jerković[3], Milica Janković[2], Dejan Stevanović[1], Blažo Nikolić[1], Mirjana B. Popović[2], [4], and Jasna Jančić[1], [5]

1Clinic for Neurology and Psychiatry for Children and Youth, Belgrade, Serbia;
2School of Electrical Engineering, University of Belgrade, Serbia;
3Innovation Center, School of Electrical Engineering, University of Belgrade, Serbia;
4Institute for Medical Research, University of Belgrade, Serbia;
5Faculty of Medicine, University of Belgrade, Serbia

nikola.ivancevic.npk@gmail.com

Aims: Pediatric onset multiple sclerosis (pedMS) is a chronic, autoimmune, inflammatory, neurodegenerative and demyelinating disease of the central nervous system. In adults with MS writing is affected due to the sensory-motor and cognitive impairment. Compared to healthy controls (HC) they write with higher movement duration, fragmented velocity profile and higher jerk. To the authors' best knowledge there are no data regarding writing performance in pedMS.

The aim was to test writing kinematic of pedMS patients in comparison with HC.

Methods: 10 pedMS subjects with neurological signs only (without disability) and 10 matched HC were enrolled. All subjects wrote cursive letter "ll" in two rectangles of different height (40 x 160 and 9 x 160 mm) on a digitizing board with ink stylus.

Results: PedMS compared to HC made writing strokes of greater duration (77:56 ms, 40 mm conditions, p=0.04; 82:54 ms, 9 mm conditions, p=0.03) and length (1.9:1.4 mm, 40 mm conditions, p=0.02; 1.4:0.9 mm, 9 mm conditions, p=0.03). They showed higher acceleration; made more changes in velocity and acceleration; over- and undershoot more often writing boundaries.

Conclusions: PedMS writing differed significantly compared to HC. PedMS subjects wrote less "smooth" (made bigger and longer strokes with higher acceleration and jerk); less automated (greater number of changes in velocity and acceleration); and less precise (more hypo- and hypermetric movements).

Writing performance is affected in pedMS compared to HC. Writing kinematic is a potential additional neuropsychological assessment during follow-up of subjects with pedMS.

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AMYLOID- B ACCUMULATION ALTERS CHOLESTEROL-RELATED GENE EXPRESSION AND AFFECTS THE VISUAL CYCLE IN MOUSE RETINA AND RPE OF APP KNOCK-IN MICE

Sanja Ivkovic[1], Arnout Bruggeman[2,3], Charysse Vandendriessche[2,3],, Selma Kanazir[1] and Roosmarijn E. Vandenbroucke[2,3]

1Institute for Biological research "Sinisa Stankovic", University of Belgrade, Serbia;
2Barriers in Inflammation lab, VIB Center for Inflammation Research, VIB, Belgium;
3Department of Biomedical Molecular Biology, Ghent University, Belgium

sanja.ivkovic@ibiss.bg.ac.rs

Aims: Amyloid-β has been implicated as a key player in the progression of age-related macular degeneration (AMD). The $APP^{NLG-F/NLG-F}$ knock-in mouse, characterized with the accumulation of amyloid-β (Aβ), without the phenotypes related to the amyloid precursor protein (APP) overexpression, is considered as the true "preclinical" model. However, retinal pathology in this mouse model is still undetermined. Aβ has an essential physiological role in lipid homeostasis causing a decrease in cholesterol synthesis. Conversely cholesterol increases Aβ production. We hypothesized that the over production of Aβ will have an effect on the cholesterol-related gene transcriptional network. As the changes in cholesterol metabolism have been implicated in the pathogenesis of AMD, these analyses can deepen the understanding of the effects of Aβ on the cholesterol homeostasis in retina and RPE.

Methods: We used real-time PCR to quantify the expression levels of genes regulating biosynthesis, transport, and elimination of cholesterol and its metabolites in retina and RPE, from 7- and 40-week-old control and APPNLG-F/NLG-F(). As a functional outcome we analyzed the expression profile of visual cycle genes in RPE.

Results: Our study reveals that the retina and RPE in APPNLG-F/NLG-Fmice exhibit significant changes in cholesterol-related transcriptional networks. Finally, we observed a significant decrease in the expression levels of the key regulatory genes of the visual cycle in RPE.

Conclusions: The studies of Aβ associated changes in the transcriptional networks in the retina have the potential to offer new insights into AMD development and progression.

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P054

SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW, POTENTIAL MAO-B LIGANDS

Ivana I. Jevtić[1], Thu Hang Lai[2], Jelena Z. Penjišević,[1] Rodrigo Teodoro[2], Sladjana Dukic-Stefanovic[2], Peter Brust[2], Slađana V. Kostić-Rajačić[1]

1Institute of Chemistry, Technology and Metallurgy, Department of Chemistry, University of Belgrade, Serbia;
2Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research, Department of Neuroradiopharmaceuticals, Research site Leipzig, Germany

ikajevticeva@gmail.com

The aim of this study was to develop highly specific radiofluorinated ligands for quantitative positron emission tomography (PET) imaging of monoamine oxidase-B (MAO-B) in brain.

A series of 8 fluoro derivatives of 1-cinnamyl-4-arylpiperazine were synthesized by standard methods of organic synthesis. The affinity of the compounds was determined in a competitive binding assay using L-[3H] deprenyl as radioligand on rat brain homogenates. The KD of the radioligand was determined by homologous competition.

An efficient, three-step procedure for the synthesis of the potential MAO-B ligands was developed. A competitive binding assay was established, using L-[3H]deprenyl as the radioligand, and rat brain membrane homogenate. The compounds were screened (three concentrations 10-9, 10-7 and 10-5) for their MAO-B affinity.

We successfully synthesized a series of fluorinated MAO-B ligands. Unfortunately, their affinities toward MAO-B have proved to be rather low. To increase the affinity further modifications are needed.

This work was supported by MNTR the Republic of Serbia (grant No. 172032) and DAAD (grant No.57391403) within the Bilateral project "Development of new fluorinated radioligands for PET imaging of monoamine oxidase B (MAO-B)"

P055

MECHANISM UNDERLYING EFFECTS OF FISH OIL SUPPLEMENTATION IN PRESYMPTOMATIC STAGE OF ALZHEIMER DISEASE IN 5XFAD MICE

Milena Jović, Natasa Lončarević-Vasiljković, Sanja Ivković, Desanka Milanović, Selma Kanazir

Department of Neurobiology, Institute for Biological Research "Siniša Stanković", University of Belgrade, Belgrade, Serbia

milena.jovic@ibiss.bg.ac.rs

Aims: Alzheimer's disease (AD) is the most prevalent type of dementia in elderly,triggered by multiple factors such as amyloid plaques, neurofibrillary tangles and neuroinflammation. The use of supplements with omega-3 fatty acids has been associated with reduced risk and lessened AD pathology. The purpose of this study was to elucidate the mechanisms underlying effects of short-term fish oil (FO) suplementation in presymptomatic stage of AD in 5xFAD mice.

Methods: Three-month old female 5xFAD mice received FO (100µl/animal/day) via oral gavage during the period of 3 weeks. Western blot and immunohistochemical analysis were used to detect changes in pathological features of AD in cortex of 5xFAD mice. AmiloGlo was used to visualize plaques. Amyloid beta (Aβ) peptide, dystrophic neurites (DNs), microglia/macrophages and CX3CR1/CX3CL1 were detect by anti-Aβ42-, anti-SMI31-, p-Tau-, anti-Iba-1-, anti-CX3CR1 anti-CX3CL1 antibodies, retrospectively. Immunostaining was observed by confocal microscopy. Quantification was done by Image J and Image Quant softwer.

Results: The present study shows that short-term FO supplementation applied in presymptomatic stage of AD, alters the behaviour of microglia/macrophages prompting them to establish a physical barrier around amyloid plaques. This barrier significantly suppresses DNs formation through the reduction of both Aβ content and tau hyperphosphorylation. Moreover, the short-term FO treatment suppresses CX3CR1/CX3CL1 axis, interaction between microglial cells and neurons, which represents one of possible mechanisms for altered microglial/macrophage motility and colocalization around plaques.

Conclusion: Our findings suggest that FO consumption may play an important role in modulating microglial response and ameliorating the AD pathology in presymptomatic stage of Alzheimer's disease.

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P056

DEVELOPMENT OF AUTOMATED ANALYSIS OF BIOMEDICAL SIGNALS SUCH AS CALCIUM IMAGING

Andrej Korenić[1], Gizem Dursun[2], Dunja Bijelić[1], Katarina Milićević[1], Milena Milošević[1], Lidija Radenović[1], Ufuk Özkaya[2], Bilal Ersen Kerman[3], Pavle R. Andjus[1], Abdulkerim Çapar[4]

1Institute of Physiology and Biochemistry, Faculty of Biology, University of Belgrade,Belgrade, Serbia;
2Süleyman Demirel University, Isparta,Turkey;
3İstanbul Medipol University, İstanbul, 4 İstanbul Technical University, İstanbul, Turkey

andrej.korenic@bio.bg.ac.rs

Aims: In a series of previous studies we demonstrated the effect of purified immunoglobulins G from ALS patients (ALS IgGs) on Ca homeostasis in rat astrocytes in culture. In order to develop automated diagnostic screening of these IgGs as compared to healthy IgGs, the raw data for the analysis came from the primary rat cortical astrocytes recorded for calcium imaging.

Methods: The first step in the automated analysis was to determine the boundaries for each cell Region of Interests (ROIs). We implemented the methods called Adaptive Histogram Equalization and Active Contour Model in order to segment the cells in the video. Secondly, in order to assess the performance of Supervised Machine Learning algorithms in discriminating between calcium traces, we extracted the same length of traces for (1) baseline (with perfusion on), (2) IgG treatment, (3) IgG wash (with perfusion on) and (4) ATP application. We also utilized Unsupervised Machine Learning algorithms in order to: (1) characterize traces and extract significant features, (2) cluster the traces and (3) if any groups could be found, train a classifier to reliably predict a class for any given test trace.

Results and Conclusions: Applied segmentation methods created a single new image making the boundaries of every cell more pronounced while also decreasing the computational cost. Clustering with Decision Trees along with Block Bootstrapping for time series to model the traces, as well as k-Nearest Neighbors classification, gave us satisfactory preliminary results for applying Majority-Voting classification and comparison with the performance of Convolutional Neural Networks.

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P057

SIMVASTATIN ATTENUATES MYELIN DAMAGE IN HIGH FAT DIET-FED C57BL/6J MICE

Tamara Kravic-Stevovic[1], Darko Ciric[1], Tamara Martinovic[1], Sasa Petricevic[2], Vladimir Trajkovic[3], Vladimir Bumbasirevic[1]

1Institute of Histology and Embryology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia;
2Faculty of Pharmacy, Novi Sad, Serbia;
3Institute of Microbiology and Immunology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

tamarakravic@yahoo.com

Aims: Our research was intended to assess the effects of simvastatin on sciatic nerve damage in high fat diet (HFD) mouse model of metabolic syndrome and type 2 diabetes.

Methods: In this study male C57BL/6J mice were used. The control group was fed with a standard chow and the other two with a HFD for 6 months. During the last month, once a day, mice fed with HFD were given simvastatin orally. Sciatic nerve samples were dissected and processed for transmission electron microscopy (TEM). Samples were fixed in glutaraldehyde and osmium tetroxide, and embedded in Epoxy resins. Ultrathin sections were examined on a TEM.

Results: TEM analysis showed that in the control group the majority of axons were without any signs of alteration. In other groups, these alterations were more frequently present. One form of damage manifested as wide separations of myelin lamellae in the central parts of the myelin sheet. Other ultrastructural alterations manifested as wide axon myelin separations at the interface of Schwann cells and the axoplasm, containing what appeared to be various cellular material and myelin figures. Mice fed with HFD had higher numbers of ultrastructurally altered myelinated axons than control animals ($P<0.05$). Simvastatin reduced number of damaged myelinated fibers to the level seen in control mice. Myelination of nerve fibers was assessed using g-ratio calculation and there was no statistically significant difference between different groups.

Conclusions: Results of these experiments emphasizes neuroprotection as another rationale for usage of simvastatin in metabolic syndrome and diabetes type 2.

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P058

THE EFFECT OF H2S DONOR GYY4137 ON ENCEPHALITOGENIC IMMUNE CELLS

Milica Lazarević[1], Maria Sofia Basile[2], Paolo Fagone[2], Ferdinando Nicolleti[2], Đorđe Miljković[1], Miljana Momčilović[1]

1Department of Immunology, Institute for Biological Research "Siniša Stanković", University of Belgrade, Belgrade, Serbia;
2Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy

milica.laza93@gmail.com

Aims: GYY4137 is a slow-releasing donor of H2S, a molecule shown to exert anti-inflammatory effects. Considering the importance of inflammatory component in the pathogenesis of multiple sclerosis, a chronic demyelinating CNS disease, and its animal model experimental autoimmune encephalomyelitis, here we aimed to determine the in vitro effects of GYY4137 on encephalitogenic immune cells.

Methods: Rats were immunized with an encephalitogenic emulsion and draining lymph node cells (DLNC) and spinal cord immune cells (SCIC) were isolated. CD4+ T cells were isolated by magnetic separation. After 24h exposure of immune cells to GYY4137 (200μM), cytokine production was determined by ELISA. For phenotypic characterization, cells were treated with GYY4137 for 40 min and subsequently analyzed by cytofluorometry. Cell viability was evaluated by MTT.

Results: Having no effect on cell viability, GYY4137 reduced IFN-γ and IL-17 production in DLNC and SCIC. However, GYY4137 didn't exert effects on the percentage of IL-17+ cells within CD4+ DLNC and SCIC. On the other hand, treatment with GYY4137 reduced the percentage of FoxP3+ cells in the CD4+ population of DLNC and SCIC, as well as in CD4+ T cells purified from DLNC. These results suggest that GYY4137 negatively affects regulatory T cell population at the periphery and in the target tissue, but that it also reduces the ability of the encephalitogenic cells to generate IFN-γ and IL-17.

Conclusion: Further studies on the relevance of the observed results for the pathogenesis of multiple sclerosis, as well as on the mechanisms behind them are warranted.

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THE FREQUENCY OF C9ORF72 REPEAT EXPANSION BEYOND ALS/FTD SPECTRUM IN SERBIAN PATIENTS WITH NEURODEGENERATIVE DISORDERS

Marjanović Ana[1,2], Dobričić Valerija[1], Branković Marija[1,2], Janković Milena[1], Mandić Gorana[1,2],Lukić Ječmenica Milica[1],Stefanova Elka[1,2],,Stević Zorica[1,2], Novaković Ivana[1,2], Kostić Vladimir[1,2]

1Neurology Clinic, Clinical Center of Serbia, Belgrade, Serbia;
2School of Medicine, University of Belgrade, Belgrade, Serbia

ana.marjanovic@yahoo.com

Aims: Since discovering, hexanucleotide repeat expansion (GGGGCC) in C9orf72 gene was firmly related to amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). In the past few years, phenotypic spectrum of this expansion is widening to other neurodegenerative disorders with variable frequencies. In our study we have analyzed the number of C9orf72 repeats in cohort of ALS/FTD patients and additionally in patients clinically diagnosed with Alzheimer's disease (AD), Huntington disease like (HD like) syndrome, Multiple system atrophy (MSA) and Progressive supranuclear palsy (PSP).

Methods: Cohort of patients having ALS (325), FTD (276), AD (197), HD like (143), MSA (44) and PSP (63), was analyzed to estimate the number of repeats in C9orf72 gene following 2-step protocol. Normal alleles were determined by standard PCR amplification of the region containing repeats and fragment analysis. Repeat-primed PCR was performed for all samples presenting single amplification product. We used 30 repeats as pathogenic cut-off size. In addition, Southern blot analysis was performed for most of the samples showing expansion.

Results: The expansion in C9orf72 gene was detected in 14 (4.31%) ALS, 6 (2.17%) FTD and 1 (0.70%) HD like patients. One (0.51%) AD patient had borderline repeats number. No expansion was observed in MSA and PSP group.

Conclusions: According to our results C9orf72 repeat expansion is the most frequent in ALS and FTD patients. We did not identify any repeat expansion among MSA and PSP patients indicating that C9orf72 repeat expansion is not involved in the pathogenesis of these disorders in our population.

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POSTER SESSION 1

P061

THE EFFECT POLYETHYLENE GLYCOL-COATED GOLD NANOPARTICLES ON ULTRASTRUCTURAL MORPHOLOGY OF SPINAL CORD AFTER INJURY

Tamara Martinovic[1],*, Darko Ciric[1], Tamara Kravic-Stevovic[1], Florentia Papastefanaki[2], Igor Jakovcevski[3],[4], Nafsika Poulia[2], Nevena Djogo[3], Florian Schulz[5], Gabrielle Loers[3], Tobias Vossmeyer[5], Horst Weller[5],[6], Melitta Schachner[7], Rebecca Matsas[2], Vladimir Bumbasirevic[1]

1Institute of Histology and Embryology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia;
2Laboratory of Cellular and Molecular Neurobiology, Hellenic Pasteur Institute, Athens, Greece;
3Zentrum für Molekulare Neurobiologie, Universitätsklinikum Hamburg-Eppendorf, Universität Hamburg, Hamburg, Germany;
4Experimental Neurophysiology, University Hospital Cologne, Köln, Germany;
German Center for Neurodegenerative Diseases, Bonn, Germany;
5Institut für Physikalische Chemie, Universität Hamburg, Hamburg, Germany;
6Department of Chemistry, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia;
7Center for Neuroscience, Shantou University Medical College, Shantou, Guandong, People's Republic of China

sapphire.tm@gmail.com

Aims: The aim of this study was to evaluate effects of Polyethylene Glycol-coated Gold Nanoparticles (PEG-AuNPs) on morphology of spinal cord after injury with the use of transmission electron microscopy.

Methods: At early stages after mouse spinal cord injury PEG-AuNPs dispersed in 1µl PBS were injected intraspinally 0.5 mm rostral and caudal to the lesion site, 1 mm deep into the spinal cord. Eight week after injury, mice were anaesthetized and perfused transcardially with a mixture of 4% paraformaldehyde and 2.5% glutaraldehyde. Tissue samples were cut at a distance of approximately 1 mm proximal and distal to the center of the lesion. For transmission electron microscopy samples were post-fixed in osmium tetroxide, dehydrated and embedded in epon resin. Ultrathin sections were prepared on a Leica Ultracut UCT microtome and stained with uranyl acetate-lead citrate. Ultrastructural analysis of spinal cord was performed on a FEI Morgagni 268D transmission electron microscope.

Results: PEG-AuNPs were detected as electron dense particles with an approximate 40-nm diameter size throughout the tissue of the spinal cord around the lesion site. They were associated with the plasma membranes or localized intracellularly. In the analyzed regions of spinal cord no alterations in ultrastructure of the white matter and neuron were detected in the close proximity to the PEG-AuNPs.

Conclusions: PEG-AuNPs promoted hind limb motor recovery after internalization in the spinal cord tissue. Since no ultrastructural alteration of the spinal cord, PEG-AuNPs could represent a favorable drug-delivery platform with therapeutic potential.

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P062

EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS DISTURBS THE REGULATION OF HPG AXIS IN RATS OF BOTH SEXES

Ana Milosevic[1], Marija Janjic[1], Irena Lavrnja[1], Danijela Savic[1], Marija Jakovljevic[1], Sanja Pekovic[1], Ivana Bjelobaba[1]

1 Department of Neurobiology, Institute for Biological Research "Sinisa Stankovic", University of Belgrade, Belgrade, Serbia

anamilosevic14@hotmail.com

Aims: Multiple sclerosis (MS) is a chronic neuroinflammatory disease, more common in women than in men. Because the effects of MS on hypothalamo-pituitary-gonadal axis haven't been completely elucidated, our aim was to investigate the impact of experimental autoimmune encephalomyelitis (EAE) on reproductive functions in rats.

Methods: EAE was actively induced in Dark-Agouti rats of both sexes. Disease symptoms, weight changes, and estrous cycle phase were assessed daily. The animals were sacrificed at the onset, peak, and end of EAE. Hypothalamic, pituitary and gonadal tissues were dissected for qRT-PCR and/or protein extraction. Blood was collected for hormone measurements. In separate experiments, animals at the peak of EAE and naïve controls received an injection of a GnRH analogue - buserelin.

Results: Our results suggest hypothalamic neuroinflammation in both sexes; upregulation of mRNA for several genes was registered during EAE. Hypothalamic expression of Kiss1 and Gnrh, as well as pituitary expression of Lhb, Fshb and Gnrhr mRNA, were affected differently in males and females. LH levels drop transiently following the course of EAE, coinciding with the arrest in diestrus in females and a drop in testosterone levels in males. Buserelin increased LH levels in both sexes. Additionally, StAR – a protein with a critical role in steroid hormone biosynthesis, had an opposite pattern of expression in ovaries and testicular interstitial cells during the disease, both on mRNA and protein level.

Conclusion: Our data indicate that EAE noticeably affects the regulation of HPG axis. Further analyses are needed to explore the details of this phenomenon.

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P063

HIGHER CONCENTRATION OF INTERLEUKIN 6 AND TRANSFORMING GROWTH FACTOR BETA IN PATIENTS WITH MAJOR DEPRESIVE DISORDER WITH AND WITHOUT CHILDHOOD ABUSE EXPIRIENCE

Ana Munjiza[1], Milutin Kostic[1,3], Ivanka Markovic [2,3], Dusica Lecic Tosevski,[1,3,4]

1Institue of Mental Health;
2Institute for Biochemistry;
3School of Medicine, University of Belgrade;
4Serbia academy of science and art Belgrade, Serbia

ani_0902@yahoo.com

Introduction:There has been little research into the correlation between interleukin 6 (IL6) and transforming growth factor beta (TGF-β) with childhood abuse and neglect in patients with depressive disorder (Davis et al., 2019, *Lu et al., 2013*) which are predictors of developing affective disorders in adulthood (Infurna et al, 2016).

Aim of this research was to analyze differences between serum concentrations of IL 6 and TGF-β in patients with major depresive disorder vs. healthy controls, and to investigate possible correlations with adverse childhood expiriencies.

Methods: ELISA technque was perfored for detection of serum levels of IL-6: in 64 patients and 57 healthy controls, and for TGF-β: 55 patiens and 45 healthy controls. Participants fulfilled the Beck Depression Inventory (BDI) as well as Childhood Trauma Questioner (CTQ).

Results: The concentrations of IL6 and TGF-β were significantly higher in patients with major depressive disorder, comparing to healthy controls. CTQ total scores and scores of clinical CTQ subscales concerning physical and emotional abuse, as well as physical neglect significantly correlated with serum levels of IL6. There weren't significant correlations between total CTQ score or subscale scores and TGF-β serum levels, although we found a positive trend in correlation for emotional and physical neglect (p=0.073 i p=0.071).

Conclusions: Interleukin 6 and transforming growth factor beta could be an important developmental mediator linking childhood abuse and neglect with development of depressive disorders in adolthood.

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P064

ASTROCYTE ACTIVITY IN THE CENTRAL NERVOUS SYSTEM AUTOIMMUNITY

Ljiljana Nikolic[1], Dunja Bijelic[2], Milica Lazarevic[1], Katarina Milicevic[2], Miljana Momcilovic[1], Jelena Bogdanovic Pristov[3], Branka Petkovic[1], Pavle Andjus[2], Djordje Miljkovic[1]

1Institute for Biological Research "Siniša Stanković", University of Belgrade, Serbia;
2Center for Laser Microscopy, Faculty of Biology, University of Belgrade, Serbia;
3Department of Life Sciences, Institute for Multidisciplinary Research, University of Belgrade, Serbia

nikolic13@gmail.com

Aims: Multiple sclerosis (MS) is an inflammatory autoimmune disorder of the central nervous system (CNS). Complex interactions between infiltrating immune cells (IIC) and resident glial cells of the CNS cause myelin loss and neuronal dysfunction in MS. Here we aim to understand how naïve astrocytes functionally respond to the IIC invasion of the CNS.

Methods: We measured calcium activity of naïve astrocytes in culture upon application of IIC. An experimental autoimmune encephalomyelitis (EAE) MS rat model was used to isolate IIC from the spinal cord of animals at the symptomatic stage. Naïve astrocytes were isolated from the spinal cord of WT rats.

Results: We show that IIC and not the lymph node immune cells evoke vigorous increase in the astrocyte calcium activity. This IIC-induced calcium response depends on an autocrine activation of the purinergic P2X7 receptors on the naïve astrocytes. We also show that IIC induce ATP release from astrocytes by a mechanism that involves gap junctions and/or hemichannels activation and not the vesicular pathway. Our data indicate that ATP release and subsequent increase in the astrocytic calcium activity mainly depends on the cell-cell contact between naïve astrocytes and IIC.

Conclusions: These results show that naïve astrocytes functionally respond to the IIC by augmented release of ATP. An increase in ATP release would alter astrocyte-neuron communication and affect neuronal function in MS.

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P065

RELATIONSHIP BETWEEN REGIONAL DISTRIBUTIONS OF CYTOCHROME C OXIDASE AND COPPER-DELIVERING CHAPERONES IN SCLEROTIC HIPPOCAMPI OF EPILEPSY PATIENTS

Miloš Opačić[1],*, Maja Zorović[2], Danijela Savić[3], Marko Živin[2], Savo Raičević[4], Vladimir Baščarević[4], Aleksandar Ristić[5], Dragoslav Sokić[5], Ivan Spasojević[1]

1Department of Life Sciences, Institute for Multidisciplinary Research, University of Belgrade, Belgrade, Serbia;
2Brain Research Laboratory, Institute of Pathophysiology, Medical Faculty, University of Ljubljana, Ljubljana, Slovenia;
3Department of Neurobiology, Institute for Biological Research 'Siniša Stanković', University of Belgrade, Belgrade, Serbia;
4Neurosurgery Clinic, Clinical Center of Serbia, Belgrade, Serbia;
5Center for Epilepsy and Sleep Disorders, Neurology Clinic, Clinical Center of Serbia, Belgrade, Serbia

milos@imsi.bg.ac.rs

Aims: A drop in copper level and the loss of energy homeostasis are both portrayed in mesial temporal lobe epilepsy (mTLE) with hippocampal sclerosis (HS) patients. Cytochrome c oxidase (COX) represents a crossroad of energy and copper metabolism; it is a key component of mitochondrial machinery and contains two copper centers. Our aim here was to examine the link between COX activity and the copper transporting system in HS. COX activity and the levels of mRNA of selected chaperones - COX11, COX17, Sco1 and Sco2 were determined in 13 anatomically distinct hippocampal regions.

Methods: Study was performed on seven hippocampal samples, four of which had been acquired during the course of amygdalohippocampectomy treatment of medically intractable epilepsy and three control postmortem samples. Adjacent slices were used for Nissl staining, COX activity assay and mRNA in situ hybridization with autoradiography. Densitometry was performed using ImageJ.

Results: Overall COX activity was decreased in HS compared to controls ($P = 0.0003$). However, 5 regions showed significantly lower COX activity in HS and 8 did not. Subiculum showed slightly higher activity in HS. The levels of mRNA levels were lowered in HS in 6 regions for COX11, 10 regions for COX17, two regions for Sco1 and 11 regions for Sco2.

Conclusions: Our findings suggest the loss of energy homeostasis in HS may be related to pathological changes in specific components of copper delivery to COX, and that the impact may vary between different hippocampal regions.

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P066

THE INFLUENCE OF POLYMORPHISMS IN COMT, DAT (SLC6A3), DRD2, AND ANKK1 GENES ON THE ONSET OF COMPLICATIONS OF LONG-TERM USE OF LEVODOPA IN INDIVIDUALS WITH PARKINSON'S DISEASE

Radojević B[1], Dragašević-Mišković NT[2], Marjanović A[2], Dobričić V[3], Milovanović A[2], Svetel M[2], Petrović I[2], Savić M[4], Jančić I[4], Novaković I[2], Kostić VS[2]

1Special Hospital for Cerebrovascular Disorders Saint Sava, Belgrade, Serbia;
2Clinic of Neurology, CCS, Faculty of Medicine, University of Belgrade, Serbia;
3Lübeck Interdisciplinary Platform for Genome Analytics (LIGA), Institutes of Neurogenetics & Cardiogenetics, University of Lübeck, Lübeck, Germany;
4Faculty of Pharmacy, University of Belgrade, Serbia

branka022@yahoo.co.uk

Background: Long-term use of levodopa in treatment of Parkinsonon's disease, as well as the progression of the disease, leads to the development of a number of complications such as: motor response fluctuations, dyskinesia, hallucinations. Recent studies described connection between polymorphisms in genes that are related to dopamine metabolism and dopamine transport with complications of long-term levodopa treatment.

Aim: The aim of our study was to determine the relationship of polymorphisms in COMT, DAT (SL6A3), DRD2, and ANKK1 and treatment complications such as motor fluctuations, dyskinesias, psychosis, and hallucinations.

Patients and methodes: The study included 230 patients with Parkinson's disease who were treated with levodopa for at least two years. For the evaluation of hallucinations and psychosis, we used the following scales: Neuropsyhiatric inventory, Brief Psychiatric Rating Scale, Positive and negative syndrome scale, and Tottori University Halucinattion Rating Scale. Genotyping was performed using TaqMan SNP genotyping assays (ThermoFisher Scientific, Foster City, CA) on the ABI Prism 7500 Fast Real-Time PCR System (Applied Biosystems, USA).

Results: The overall percentage of patients who developed hallucinations during illness was 46%. Patients with hallucinations were more likely to have motor complications in the form of dyskinesias and fluctuations in the motor response ($p<0.01$). In adition, patients with A-allele of rs2283265 (DRD2) had significantly lower risk for development of hallucinatios ($p<0,01$).

Conclusion: Variants in the DRD2 gene may be a protective factor for the development of hallucinations. Such findings contribute to the personalized treatment of patients with Parkinson's disease and highlight the importance of genotyping of relevant SNPs prior to therapeutic decisions.

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P067

G-PROTEIN AND MAPK/CREB1 SIGNALING AS MEDIATORS BETWEEN STRESS EXPERIENCE AND PTSD SYMPTOMS

Savić Danka[1], Adžić Miroslav[2]

1University of Belgrade, VINCA Institute of Nuclear Sciences, Laboratory of Theoretical and Condensed Matter Physics 020/2, Mike Petrovica Alasa 12-14, 11001 Belgrade, Serbia;

2University of Belgrade, VINCA Institute of Nuclear Sciences, Laboratory of Molecular Biology and Endocrinology 090, Mike Petrovica Alasa 12-14, 11001 Belgrade, Serbia

danka.s@sbb.rs

Aims: Posttraumatic stress disorder (PTSD) is a serious mental condition triggered by traumatic events. Understanding the biology of the disorder is essential for defining new therapeutic strategies. The purpose of this study was to identify some of the genes and pathways leading from stressors to the disease.

Methods: 263 male subjects were categorized in four groups: A) current PTSD (n = 68), B) lifetime PTSD (n = 42), C) trauma controls (n = 74), and D) healthy controls (n = 79). We examined gene expression profiles of G-protein (GNAS, GNAI, RGS2, ARRB1, ARRB2) and MAPK/CREB1 (MAPK14, MAPK1, MAPK3, DUSP1, CREB1) signaling in the subjects' peripheral blood mononuclear cells. One-way ANOVA, correlation analyses, linear regression and structural equation modeling (SEM) were used to define the associations of genes with stressors and PTSD symptoms.

Results: The level of RGS2 is significantly lower in the current PTSD group than in trauma and healthy control groups. The level of CREB1 is signficantly higher in PTSD than in trauma controls. Linear regression model (F=39,456, p<0,000) indicated that 42% of variance in PTSD symptoms is explained by CREB1, DUSP1, and stressors. SEM shows that stressors, G-protein and MAPK/CREB1 signaling explains 43% of the variance in PTSD symptoms. In particular, stressors act upon RGS2 and MAPK14 which further affect PTSD symptoms via MAPK/CREB1 signaling.

Conclusion: According to the measured mRNA levels, stressors exert their influence on PTSD development via G-protein and MAPK14, with the participation of MAPK1, MAPK3, DUSP1, and CREB1.

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P068

THE EFFECT OF INTERMITTENT FEEDING ON THE NUMBER OF PARVALBUMIN-EXPRESSING NEURONS IN THE HIPPOCAMPUS OF 5XFAD MICE

Maja Srbovan, Ksenija Prpa, Vesna Tesic, Desanka Milanovic, Milka Perovic, Selma Kanazir

Laboratory for Molecular Neurobiology, Department of Neurobiology, Institute for Biological Research "Siniša Stanković", University of Belgrade, Serbia

maja.srbovan@ibiss.bg.ac.rs

Aim: Food restriction has been widely associated with beneficial effects on brain aging and age-related neurodegenerative diseases such as Alzheimer's disease (AD). In the present study, the effects of every-other-day (EOD) feeding regimen were studied in the hippocampus of 5XFAD mice, a well characterized animal model of AD. Parvalbumin (PV) inhibitory interneurons that are crucial for maintaining proper excitatory/inhibitory balance were examined.

Methods: Female 5xFAD mice (Tg) and their non-transgenic littermates (non-Tg) were exposed to ad libitum (AL) or intermittent, EOD feeding regimen, beginning at 2 months of age. Neurons expressing PV were detected by immunohistochemistry, in the dorsal hippocampus of 6-month-old animals. The number of parvalbumin-expressing neurons was determined independently in CA1, CA3, and DG hippocampal subregions.

Results: Immunohistochemical analysis revealed a substantial increase in the number of parvalbumin inhibitory neurons in the dorsal hippocampus of Tg-AL mice in comparison to non-Tg animals. In Tg-EOD mice, however, alterations in the number of PV-expressing neurons were subregion-specific comparing to Tg-AL mice of the same age.

Conlusions: The results of our study clearly indicate that PV-expressing interneurons are of importance in further understanding of neural basis of AD-like-associated cognitive impairments and EOD-induced effects in 5xFAD mouse model of AD.

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P069

LONGITUDINAL CORTICAL THICKNESS CHANGES IN GBA-RELATED EARLY PARKINSON'S DISEASE

Iva Stankovic[1], Federica Agosta[2], Vladana Markovic[1], Elisabetta Sarasso[2], Paola Valsasina[2], Igor Petrovic[1], Vladimir Kostic[1], Massimo Filippi[2,3]

1Clinic of Neurology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia,2Neuroimaging Research Unit, and 3Department of Neurology, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

idstanko139@gmail.com

Background and aims: Glucocerebrosidase gene (GBA) mutations are the greatest genetic cause of parkinson's disease (PD). Compared with noncarriers, heterozygous GBA-PD patients are characterized by an earlier age-of-onset, a better response to L-Dopa and an increased likelihood to experience cognitive symptoms, neuropsychiatric disturbances, and autonomic dysfunction. This study investigated the longitudinal changes of the cortical grey matter in PD patients with hemiparkinsonism, with (GBA-positive) and without (GBA-negative) GBA mutations.

Methods: Eleven GBA-positive PD patients with hemiparkinsonism (Hoehn and Yahr 1.0 or 1.5) were compared with 24 GBA-negative PD patients matched for age, sex, disease duration and severity. Patients underwent clinical and neuropsychological evaluations and MRI scans at baseline and once a year for 3 years. 25 healthy controls underwent evaluations at baseline. The pattern of cortical thinning was investigated in PD patients relative to healthy controls at baseline. Longitudinal cortical changes were assessed in the GBA-positive and GBA-negative PD patients.

Results: At baseline, GBA-positive PD patients showed a greater left side predominant cortical atrophy in motor, frontal, temporal and occipital areas relative to both healthy controls and GBA-negative subjects matched for disease duration and severity. Overtime, the GBA-negative group showed a higher rate of cortical thinning relative to GBA-positive patients; however, the pattern of cortical thinning in GBA-negative cases did not reach the severity shown by GBA-positive patients after 3 years.

Conclusions: GBA-positive PD patients showed a greater and earlier cortical thinning relative to GBA-negative cases with the same disease duration and severity.

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P070

POSTTRAUMATIC STRESS DISORDER AND DEPRESSION IN INDIVIDUALS WITH AND WITHOUT TRAUMATIC BRAIN INJURY

M. Stevanović, M. Simonović, B. Nedović

Medical Faculty University of Nis, Nis, Serbia

markostevanovic220@yahoo.com

Background/Aim: Subjects suffering from trauma-related disorders are presenting with high rates of co-occurring posttraumatic stress disorder (PTSD), depression and traumatic brain injury (TBI). The aim of this study was to compare the clinical presentations of the war-related posttraumatic stress disorder and depression in subjects with PTSD and TBI to those with PTSD only.

Methods: 60 subjects diagnosed as PTSD were divided into two groups based on the history of TBI. The severities of the PTSD and depression in subjects with PTSD and TBI (N=37) and with PTSD only (N=23) were measured using CAPS-DX, MADRS and HDRS rating scales. Statistical analyses were performed using independent-samples t-test and multivariate analysis of variance (MANOVA) and covariance (MANCOVA).

Results: The groups presented two distinct clinical profiles, with the PTSD + TBI group endorsing significantly higher PTSD scores. The higher PTSD scores found in the PTSD + TBI group appeared to be due to higher symptom intensity across all PTSD clusters of symptoms: of reexperiencing, of avoidance and numbing and of hyperarousal PTSD symptoms, and also due to higher frequency of reexperiencing PTSD symptoms cluster. Groups did not differ on depressive psychopathology.

Conclusion: The history of TBI is associated with more severePTSD and more intense PTSD symptoms, indicating the need for careful evaluation of history of TBI in every subject suffering from PTSD to determine different treatment approaches for PTSD with comorbid TBI.

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P71

CONCOMITANT BRAIN PATHOLOGIES HAVE NO MAJOR IMPACT ON CLINICAL MILESTONES IN PROGRESSIVE SUPRANUCLEAR PALSY

Milica V. Jecmenica-Lukic, [1,2],* Carolin Kurz, [1,3],* Gesine Respondek, [1,4] Grau-Rivera Oriol [5,6] Compta Yaroslau, [7,8] Ellen Gelpi, [5,9] Claire Troakes, [10] Barcelona Brain Bank collaborative group, the MDS-endorsed PSP study group, John C. van Swieten, [11] Armin Giese, [12] Sigrun Roeber, [12] Thomas Arzberger, [1,3,12]*, Günter Höglinger, [1,4,13]*

1 German Center for Neurodegenerative Diseases (DZNE), Munich, Germany;
2 Clinic of Neurology, CCS, University of Belgrade, Republic of Serbia;
3 Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Germany;
4 Department of Neurology, Klinikum rechts der Isar, Technical University of Munich, Germany;
5 Neurological Tissue Bank of the Biobanc-Hospital Clinic-Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Catalonia, Spain;
6 Barcelonaβeta Brain Research Center, Pasqual Maragall Foundation, Barcelona, Catalonia, Spain;
7 Parkinson's Disease and Movement Disorders Unit, Department of Neurology, Hospital Clinic de Barcelona / IDIBAPS; Institut de Neurociències - Universitat de Barcelona;
8 Centro de Investigación Biomédica en Red de enfermedades Neurodegenerativas (CIBERNED);
9 Institute of Neurology, Medical University of Vienna, Vienna, Austria;
10 London Neurodegenerative Diseases Brain Bank, Institute of Psychiatry, London, United Kingdom;
11 Department of Neurology, Erasmus Medical Centre, Rotterdam, The Netherlands;
12 Center for Neuropathology and Prion Research, Munich, Germany;
13 Dept. of Neurology, Hannover Medical School, Hannover, Germany

* equal contribution

Background: To analyze the influence of concomitant brain pathologies on the highly variable clinical presentation of progressive supranuclear palsy (PSP) we analyzed the frequency and severity of co-pathologies and their impact on the clinical presentation and progression in PSP.

Methods: We examined clinical and neuropathological features of 101 pathologically confirmed PSP patients. Diagnoses and stages of co-pathologies were established according to standardized criteria, including Alzheimer's disease, argyrophilic grains, Lewy-related pathology, TDP-43 pathology, FUS pathology, cerebral amyloid angiopathy and small vessel disease. Demographic data and major clinical disease milestones of PSP (frequency and latency to onset) were extracted from patients files.

Results: Only 8% of 101 patients presented without any co-pathology. Alzheimer's disease-related pathology was the most frequent co-pathology (84%), followed by argyrophilic grains (58%), both occurring as single co-pathology or in combination with other proteinopathies or with cerebrovascular disease. Lewy-related and TDP-43 co-pathology occurred rarely (8% and 6%, respectively). FUS-positive cases could not be identified. While being common, co-pathology was mostly mild in severity, with the exception of frequently widespread argyrophilic grains. Small vessel disease was also frequent (65%) with the majority of cases exhibiting mild to moderate stages. Cerebral amyloid angiopathy (25%) occurred only in the presence of Alzheimer's disease-related changes. All these co-pathologies did not have major impact on disease milestones.

Conclusions: In PSP, concomitant neurodegenerative proteinopathies or cerebrovascular diseases are frequent, but generally mild in severity, and without striking effect on the clinical presentation. This finding underscores that 4R tau pathology drives clinical symptoms in PSP. This represents relevant information for the development of disease-modifying therapies.

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P072

DOSE-EFFECT OF ALS IGG ON CALCIUM TRANSIENTS IN CULTURED ASTROCYTES

Aleksa Vasic[1], Dunja Bijelić[2], Katarina Milićević[2], Irena Živković[3], Zorica Stević[4], Milena Milošević[2], Pavle Andjus[2]

1Faculty of Biology, University of Belgrade, Serbia;
2Center for Laser Microscopy, Faculty of Biology, University of Belgrade, Serbia;
3Immunology Research Centre "Branislav Jankovic´", Institute "Torlak", Serbia;
4Clinic of Neurology, School of Medicine, University of Belgrade, Serbia

aleksavasic96@gmail.com

Aims: Previously we demonstrated that IgG isolated from ALS patients induce a transient increase of intracellular calcium in cultured astrocytes. The aim of this study was to investigate the effect of IgG concentration on the kinetics of calcium responses.

Methods: Immunoglobulin G fraction was purified from sera of ALS patients as well as from diseased and healthy controls. Cortical astrocytes were isolated from neonate Wistar rats. Calcium imaging was performed on cells loaded with Fluo-4 AM calcium indicator and fluorescence data, representing the intracellular free calcium concentration were expressed as ΔF/F0, where ΔF represents the change in fluorescence emission and F0 the fluorescence baseline level.

Results: At concentrations greater than 50 μg/ml of ALS IgG samples, most of the astrocytes respond with elevation of intracellular calcium, whereas at lower concentrations fewer cells respond. The maximum amplitude and integrated area of the response increase with rising concentrations of ALS IgG. One sample evoked a similar response at all applied concentrations. This response was modest compared to the other tested ALS IgG and more similar to the only CTRL IgG (patient diagnosed with polyneuropathy) that evoked intracellular calcium changes.

Conclusions: Our findings indicate that different ALS IgG samples vary in their ability to induce calcium signaling in astrocytes. In most cases, the fraction of responsive astrocytes and the shape of the response are dependent on the dose of ALS IgG. The current study will elucidate further the underlying mechanisms and potential correlation with other disease parameters.

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P073

BLOOD CELLS STIMULATED BY EARLY REMOTE HIND LIMB ISCHEMIA ARE CAPABLE TO SECRETE BIOREACTIVE SUBSTANCE WITH NEUROPROTECTIVE PROPERTIES

Petra Bonová[1], Miroslava Némethová[1], Jana Jachová[1], Martin Bona[2], Ľubica Mačáková[1], Rastislav Mucha[1], Miroslav Gottlieb[1]

1Institute of Neurobiology, Biomedical Research Center SAS, Slovak Republic;
2Department of Medical Physiology, Faculty of Medicine, P.J. Safarik University, Slovak Republic

kravcukova@saske.sk

Recently it was shown that the stimuli that induce brain tolerance to ischemic condition is proteinaceous and to the site of injury is transported via circulating blood. In present study, we investigated the secreting potential of stimulated blood cells, i.e. whether the bioreactive protein substance (tolerance inducing factor) is integral part of the blood cells or is released to extracellular space.

The model of remote hind limb ischemia in rats was used to mediate production of tolerance induction factor in blood cells. Blood samples were collected one hour later, original blood plasma was substituted by artificial one and incubated in vitro for 2.5 hour. The blood cells secretome was obtained after centrifugation and its neuroprotective properties were tested in vitro and in vivo as followed.

In vitro, blood cells secretome was tested on glutamate mediated toxicity model on neuronal cell population. Results showed that secretome of stimulated cells improved survival of neurons (propidium iodid incorporation, lactate dehydrogenase release) with preserved metabolic activity (MTT assay) in toxic condition of glutamate. In vivo, preischemic intravenous administration of stimulated secreome led to diminution of ischemic infarct volume mediated by transient occlusion of middle cerebral artery. Moreover, application of blood cells secretome of animals pretreated with tolerance inhibitor did not exhibit infarct reduction.

Taking together, we confirmed that proper stimulation of blood cells could lead to production and secretion of bioreactive protein to extracellular space that could induce tolerance to ischemic condition in sensitive brain tissue.

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P074

WHAT CAN PROTEOMIC PROFILING TELL US ABOUT ISCHEMIA/REPERFUSION INJURY IN HIPPOCAMPAL TISSUE?

Tomašcová A[1], Tatarková Z[1], Kalenská D[1], Lehotský J[1,2]

1Department of Medical Biochemistry, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Slovakia;
2Biomedical Center Martin, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Slovakia

benova111@uniba.sk

Aim: Global ischemic brain injury results from lack of blood flow to the entire brain. A few minutes after onset of ischaemia, brain tissue arises irreversible bioenergetic impairment. Subsequent reperfusion can cause further damage through excessive production of reactive oxygen species. We compared protein profiles of rat's hippocampus that underwent ischaemic insult with control group and group pre-treated with ischaemic preconditioning. Proteins with significant change in expression were identified to help elucidate protein mechanisms of global ischaemia and to see, if ischaemic preconditioning has neuroprotective effect on hippocampal tissue.

Methods: Adult male Wistar rats were randomly divided into control, ischemia-reperfusion (IR) and preconditioned (IPC) groups, 5 animals per group. Global ischemia was induced by 15 min of standard 4-vessel occlusion with 24-hour reperfusion. Preconditioning was induced by 5 min ischemic insult 48 hours prior IR. Hippocampal homogenates were analysed by 2D-gel electrophoresis with protein identification on MALDI-TOF mass spectrometer (Bruker).

Results: Out of 273 detected proteins, 24 were identified as significantly changed. Molecular chaperones, as Heat Shock 70kDa Protein 1, manifested high overexpression. Over twofold downregulation was observed in expression of Peroxiredoxins 5 and 6, linked to cellular redox state. Upregulated were proteins involved in glutamine metabolism - Glutamine Synthetase and Glutamine Dehydrogenase, and proteins of energy metabolism Glyceraldehyde-3P Dehydrogenase and Succinate Dehydrogenase.

Conclusion: Proteomic analysis of IR and IPC hippocampus showed modified regulation in different metabolic pathways and higher sensitivity to changes in overall redox state. Upregulation in proteins handling glutamate metabolism indicates utilization of alternative energy sources.

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P075

DIFFERENTIAL METHYLATION AND EXPRESSION OF ZNF714 AND NRIP3 IN SUICIDE VICTIMS

Katarina Kouter[1], Tomaž Zupanc[2], Alja Videtič Paska[1]

1Institute of Biochemistry, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia;
2Institute of Forensic Medicine, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

katarina.kouter@mf.uni-lj.si

Aim: Suicidal behavior is a multifactorial, polygenic state affecting millions worldwide and is a result of epigenetic interaction between hereditary and environmental factors. Despite vast knowledge on suicidality complete mechanism and factors leading to suicidal behavior are not known. However there is an indication between changes in DNA methylation patterns, differential gene expression and suicidal behavior. The aim of our study was to investigate genome-wide DNA methylation and gene expression in a high risk population.

Methods: Two homogenous groups of male suicide victims who died by hanging and control subjects were formed. Altogether our study included 18 subjects in which two brain regions BA9 and hippocampus were investigated. Using RRBS (reduced representation bisulfite sequencing) method we sequenced both regions (BA9 n = 18, hippocampus n = 12), obtaining methylation information of regions involved in gene regulation. Based on methylation level within both groups, several genes were selected and their expression was investigated using RT-qPCR.

Results: Our results have shown several differences in methylation level between suicide victims and controls in both brain regions. Additional gene ontology analysis revealed enriched GO terms for cell structural integrity and nervous system regulation. Gene expression analysis identified changes in two genes, ZNF714 and NRIP3.

Conclusion: Despite a decrease in number of suicides for the past decade Slovenia still ranks as one of the leading European countries regarding suicide rate. Our study may offer novel insights into altered epigenetic state in suicide victims.

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P076

EFFECTS OF LEVODOPA ON PROLACTIN EXPRESSION WITHIN THE ADENOHYPOPHYSIS AND 17B-ESTRADIOL-INDUCED PROLACTINOMAS IN A RAT POSTMENOPAUSAL HEMI-PARKINSONISM MODEL

Maja Zorović, Kaja Kolmančič, Marko Živin

Brain Research Laboratory, Institute of Pathophysiology, Medical Faculty, University of Ljubljana, Ljubljana, Slovenia

maja.zorovic@mf.uni-lj.si

Estrogen replacement therapy remains the most common treatment for menopausal symptoms. At the same time, there is much controversy over the role of estrogens in the pathogenesis of Parkinson's disease (PD) and levodopa-induced dyskinesias, a common unwanted outcome of the treatment of PD with levodopa. It is well known that the treatment with estrogen replacement therapy and with levodopa may also affect the pituitary gland, therefore we aimed to investigate the effects of 17-beta-estradiol (E2) and levodopa on prolactin (PRL) synthesis and on the size of pituitary gland in a rat model of postmenopausal hemi-parkinsonism.

The study was performed on ovariectomized female Wistar rats that received either E2 or empty implants. The hemi-parkinsonism model was achieved using unilateral 6-hydroxydopamine (6-OHDA) lesioning surgery. The animals then received daily injections of either levodopa or saline for two weeks. Sizes of pituitary glands were estimated from maximal sectional areas of 10 µm serial coronal sections. PRL expression was assessed using chromogenic immunohistochemistry and computerized densitometry. Serum concentrations of E2 and PRL were determined using ELISA test kits.

All animals with E2 implants showed elevated serum PRL levels and developed prolactinomas, which were significantly smaller in the treatment group receiving levodopa. Analysis of PRL immunosignal intensity revealed that E2 significantly lowered overall PRL expression, despite causing prolactinomas. L-dopa, however, had no effect on PRL expression.

These findings suggest that in our study, increased serum PRL levels in animals with E2 induced prolactinomas were predominantly the result of increase in number of lactotrophs rather than the increase in PRL expression itself.

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P077

MAGNETIC RESONANCE IMAGING IN DETECTION OF NEUROMELANIN IN SUBSTANTIA NIGRA IN PARKINSON'S DISEASE

Gašper Zupan[1], Dušan Šuput[1], Zvezdan Pirtošek[1,2], Andrej Vovk[1].

1University of Ljubljana, Faculty of Medicine, Ljubljana, Slovenia;
2University Medical Centre Ljubljana, Division of Neurology, Ljubljana, Slovenia

gasper.zupan@mf.uni-lj.si

Aims: Several studies report reduction of neuromelanin (NM) in Parkinson's disease (PD). This can be demonstrated in substantia nigra (SN), a part of mesencephalon that has a pathognomonic role in PD genesis. The aim of this study was to detect and quantify NM in SN with manual and semi-automatic methods utilizing T1-weighted spectral presaturation with inversion recovery (SPIR) images.

Material and methods: Ten patients with diagnosed PD based on patients' history and exam, and ten healthy subjects (HC) were included. T1-weighted SPIR images were acquired on a 3T scanner (Philips, Netherlands) and were used in segmentation process. Manual and semi-automatic local statistics signature-based segmentations were used to yield surface and volume of SN, respectively. ROC analysis was performed to determine sensitivity and specificity of both methods.

Results: In PD group, mean surface (40.0 +/- 9.0 vs 57.7 +/- 6.8 mm^2) and volume (261.0 +/- 28.5 vs. 398.6 +/- 100.3 mm^3) of SN were significantly lower than in the HC group. For surface, sensitivity and specificity were 90 and 90 percent, respectively. For volume, sensitivity and specificity were 90 and 100 percent, respectively.

Conclusions: Manual and semi-automatic segmentation methods can reliably distinguish between PD patients and HC. ROC analysis demonstrates high sensitivity and specificity of both methods in detection of reduced surface and volume of SN in PD.

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P078

MCT8-D2 KNOCK-OUT MICE PRESENT HYPERACTIVITY AND DEEP ALTERATIONS IN THEIR METABOLIC RATES DURING THE DARK PHASE

García-Aldea A[1], Grijota-Martínez C [1,2], Guadaño-Ferraz A [1,2].

1Instituto de Investigaciones Biomédicas Alberto Sols, Consejo Superior de Investigaciones Científicas (CSIC)-Universidad Autónoma de Madrid (UAM), Madrid, Spain;
2Center for Biomedical Research on Rare Diseases (Ciberer) Unit 708, Instituto de Salud Carlos III, Madrid, Spain

agarciaaldea@iib.uam.es

Allan-Herndon-Dudley syndrome (AHDS) is a rare disease due to mutations in the monocarboxylate transporter 8 (MCT8), a highly specific transmembrane transporter of thyroid hormones. This syndrome is characterized by an unusual thyroid hormone concentrations in blood, and a severe neurological damage most likely due to an impaired transport of T3 across the brain barriers. Mct8-deficient mice replicate the alterations in thyroid hormone levels but they do not reproduce the neurological syndrome, due to a compensatory mechanism involving the Dio2 enzyme in the brain, which converts T4 into T3.

Because of that, double Mct8-Dio2 knockout (KO) mice have been proposed as a new model for AHDS. Thyroid hormones are crucial to maintain energy homeostasis, leading to metabolic alterations when imbalanced. The aim of this work was to go in depth in the study of the metabolic state in this animal model.

We analyzed in an open circuit indirect calorimetry system the food and water intake and physical activity of Mct8-Dio2KO mice, as well as O2 consumption and CO2 production, which were used to estimate the respiratory exchange ratio (RER), total energy expenditure (TEE), and glucose and lipid oxidation.

Our results revealed a significant increase in the total activity of Mct8-Dio2KO mice, especially in the dark phase, without changes in the food and water intake. Moreover, an increase in the TEE was observed. There were no differences in the oxidation of glucose, but an increase in lipid oxidation was observed in the dark phase.

Overall our results suggest a hypermetabolic state in the Mct8-Dio2KO mice during the dark phase, together with hyperactivity phenotype, but with no differences in the food and water intake.

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P079

A RARE CASE OF FRONTOTEMPORAL LOBAR DEGENERATION CAUSED BY VARIANTS OF GRN AND CHMP2B GENES

Sevilhan Artan[1], Ebru Erzurumluoglu Gokalp[1], Demet Ozbabalik Adapinar[2], Hasan Bas[1], Oguz Cilingir[1], Beyhan Durak Aras[1]

1Eskisehir Osmangazi University, Faculty of Medicine, Department of Medical Genetics, Eskisehir, Turkey;
2Acıbadem Hospital Neurology Clinic, Eskisehir, Turkey

sartan26@gmail.com

Aims: Frontotemporal Lobar Degeneration(FTLD), is a group of clinically,pathologically and genetically heterogenous progressive brain disorder. Pathogenic variants of GRN gene are seen in 5-20% of familial FTLD cases, whereas CHMP2B mutations are rarely seen (<1%). Here, we report clinical features and segregation analysis of the FTLD case having both a rare pathogenic GRN variant and a novel CHMP2B variant.

Methods: The proband's gDNA was sequenced by using IonTorrentS5 for exons/exon-intron junctions of MAPT,GRN,CHMP2B,VCP,TARDBP and FUS genes.

Results: Clinical findings of the case firstly appeared when he was 56 with amnesia, aggressive behaviour, self-neglect, failure to achieve daily routines, sterotypical movements and she had unilateral hemiparesia. The molecular analyses revealed that phenotype of the case resulted by coccurrence of a pathogenic GRN variant (c.759_760delTG) and a novel variant (c.389A>G) that is located in conserved residues in CHMP2B gene and was defined as damaging by four in silico tools. The segregation analysis on family members showed that sister (50y) and brother (45y) of the proband also had these two variations. Daughter of the proband had GRN variant, one of the sons had both variants and the other had CHMP2B variant. All family members were asymptomatic yet.

Conclusions: Because the disease onset at an early age with a severe phenotype and died within one year of diagnosis; it is thought that the cooccurence of these variants may result with poor prognosis and reduced survival time.The interaction of various genetic factors may be a valuable prognostic marker. This study was supported by The Scientific and Technological Research Council of Turkey (TUBITAK1001-114S346)

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P080

MOTOR BEHAVIORAL CONSEQUENCES OF GESTATIONAL ANTIEPILEPTIC DRUG EXPOSURE IN RATS

Mahmut Guner[1] and Emel Ulupinar[1,2]

1Eskisehir Osmangazi University, Faculty of Medicine, Department of Anatomy, Eskisehir, Turkey;
2Eskişehir Osmangazi University, Health Science Institute, Interdisciplinary Neuroscience Department, Eskisehir, Turkey

sarilen2010@gmail.com

Aims: Since convulsive seizures negatively affect offspring development, antiepileptic treatment needs to be continued during pregnancy. In this study, we aimed to compare the effects of two different anti-epileptic drug, phenobarbital and lamotrigine having higher and lower developmental neurotoxicity potentials, respectively.

Methods: The embryonic day (E)0 was determined by sperm positivity in the vaginal smear. Pregnant rats were divided into three groups. Phenobarbital (20mg/kg), lamotrigine (20mg/kg) or saline was administered by oral gavage between E14-E21. Then, motor behaviors of pups (n= 7, for each group and gender) were evaluated by behavioral tests between postnatal day (P) 40-60.

Results: The latency to fall from a rotating rod and the total traveled distance in an open field arena are significantly lower in animals treated with phenobarbital in comparison to control and lamotrigine treatment groups. There is no significant difference among groups in the performances of elevated-plus maze and string suspension tests. On the other hand, ambulatory movements and total distance in the activity meter were significantly lower only in females treated with phenobarbital. In the skill-required grasp test, lamotrigine treated females displayed a comparable adaptation and motor learning rate to controls.

Conclusions: Our results suggest that lamotrigine treatment during pregnancy causes less detrimental effects than phenobarbital treatment on the motor coordination and learning parameters of pups during their young-adult period. Gender-dependent differences were observed especially in the spontaneous locomotor activity of animals treated with different anti-epileptic agents.

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P081

THE ROLE HYDROGEN SULFIDE (H2S) IN PENTYLENTETRAZOLE-INDUCED SEIZURE IN RATS

Cansu Kılıç[1], Kevser Erol[1], Rabiye Altınbaş[2], Hatice Doğan[3], Çiğdem Çengelli Ünel[1], Nuşin Harmancı[1], Zuhal Kaltuş[1]

1Eskisehir Osmangazi University, Faculty of Medicine, Department of Pharmacology, Eskisehir, Turkey;
2Eskisehir City Hospital, Department of Microbiology, Division of Mycology, Eskisehir, Turkey;
3Hatay Mustafa Kemal University, Faculty of Medicine, Department of Physiology, Hatay, Turkey

kiliccansu@windowslive.com

Aim: Epilepsy is a chronic disease characterized by recurrent seizures over a long period of time. More rational methods in the treatment of epilepsy must be needed. Hydrogen sulfide (H2S) is a bioactive mediator in various body systems. The neuroprotective, neuromodulator and therapeutic effects of H2S donors were previously reported. The role of H2S in seizures has been unclear. Study aimed to investigate the effects of H2S on seizure duration and latency by applying H2S donor NaHS in pentylenetetrazole (PTZ)-induced seizure.

Methods: Seizures were induced in female Wistar rats by single injection of PTZ (60 mg/kg). Twenty eight rats were divided as: control(PTZ), diazepam(D, 2mg/kg), NaHS(N5, 5 mg/kg) and NaHS(N10, 10 mg/kg). Diazepam, NaHS (5-10 mg/kg) were applied 30 minutes before PTZ injections intraperitoneally. The generalized tonic-clonic seizure (GTCS) latency, duration and mortality were recorded. SPSS 21 and Sigma Stat were used for statistical analysis and $p<0,05$ was accepted as significant

Results: Seizure latency was significantly decreased by diazepam with respect to control group ($p=0,021$). NaHS (5 mg/kg) and NaHS (10 mg/kg) do not have significant effect on latency with respect to control group. The duration of seizure was significantly decreased by diazepam and NaHS (10 mg/kg). Any significant change can not be observed in myoclonic jerk latency. In diazepam and N10 groups, there was no death however 4:7 and 2:7 rats were dead in control and N5 groups respectively.

Conclusions: NaHS seems to decrease seizure duration with respect to control (PTZ). NaHS 10 mg/kg seems to be as effective as diazepam.

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P082

NEUROPROTECTIVE EFFECT OF HUMANIN IN AN IN VITRO PARKINSON'S DISEASE MODEL

Gulgun Sengul[1,2], Seyhmus Bayar[1], Seyma Tasdemir[3],[4], Buse Kayhan[1], Aylin Sendemir[3]

1Department of Neuroscience, Institute of Health Sciences, Ege University, Izmir, Turkey;
2Department of Anatomy, School of Medicine, Ege University, Izmir, Turkey;
3Department of Bioengineering, Faculty of Engineering, Ege University, Izmir, Turkey;
4Department of Bioengineering, Faculty of Engineering and Architecture, Sinop University, Sinop, Turkey

gulgun.sengul@gmail.com

Aims: Humanin (HN), a peptide with 24 amino acids, has been studied in many neurodegenerative diseases including Alzheimer's disease after its discovery. The aim of this study was to investigate whether HN has a neuroprotective effect in an in vitro Parkinson's disease model induced by 6-hydroxydopamine (6-OHDA).

Methods: SH-SY5Y human neuroblastoma cell line was used to model Parkinson's disease in vitro. The neuroprotective effect of HN against 6-OHDA neurotoxicity was investigated through mitochondrial dysfunction, apoptosis and cytotoxicity parameters. Different concentrations of 6-OHDA (1600-100 µM) and HN (20-0.3125 µM) were applied on cells. The neuroprotective effect of HN was investigated using MTT, LDH and caspase-3 assays. Statistical analysis was performed using GraphPad Prism 8 program. The differences between the groups were evaluated with one-way ANOVA statistics.

Results: The IC50 dose was calculated as 233.7 µM. HN did not have a proliferative effect when administered alone. However, 24 h pretreatment by 10 µM and 20 µM HN showed a neuroprotective effect against 6-OHDA neurotoxicity ($p<0.01$). LDH secretion was not detected in any HN dose group. HN decreased caspase-3 levels but this difference was not statistically significant ($p>0.05$).

Conclusion: The results of this study show a HN has a neuroprotective effect of HN against 6-OHDA neurotoxicity. This should be further investigated in other in vitro and in vivo animal Parkinson›s disease models to reveal if it can be used in the treatment of Parkinson›s disease.

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P083

MOTOR BEHAVIORAL OUTCOMES OF TARGETED DELIVERY OF TAR-DNA BINDING PROTEIN-43 (TDP-43) IN UPPER MOTOR NEURONS

Emel Ulupinar[1,2], Birce Ercelen[1], Handan Acelya Kapkac[3], Elif Polat Corumlu[2], Muhittin Arslanyolu[3] ,

1Department of Anatomy, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey ;
2Department of Interdisciplinary Neuroscience, Health Sciences Institute, Eskisehir Osmangazi University, Eskisehir, Turkey;
3Department of Molecular Biology, Faculty of Sciences, Eskisehir Technical University, Eskisehir, Turkey

eulupi@ogu.edu.tr

Aims: In many neurodegenerative diseases, proteinopathy represents one of the key pathogenic mechanisms. Recently, genetic mutations in the *TARDBP* gene encoding TAR-DNA binding protein-43 (TDP-43) is associated with amyotrophic lateral sclerosis, frontotemporal dementia and Alzheimer's disease. In this study, we used adeno-associated virus (AAV) for targeted delivery and long-term expression of TDP-43 in the upper motor neurons via a single intravenous injection of the vector.

Methods: Targeted expression of TDP-43 protein in the corticospinal motor neurons of rats was achieved by a specifically designed viral expression cassette, consisting of a tissue-specific promoter ubiquitin C-terminal hydrolase-L1 (UCHL1) and the capsid (serotype-9). Other specific elements were also added to enhance transduction efficacy. Following hypothermia anesthesia, the facial vein of 3-day old Sprague-Dawley pups (n=6 for each group) were used for delivery of the viral vectors, with or without the transgene, into the systemic circulation. Motor functions and coordination of adult animals were evaluated by modified grip and rotarod tests at postnatal day 120.

Results: The latency to fall off the rotarod showed no significant difference between the control and wild-type TDP43 injected animals. However, control animals obtained significantly ($p<0.0001$) higher scores in the modified grip test.

Conclusion: Viral vector-mediated gene expression is a new and powerful tool for preclinical studies. Utilization of UCHL1, as a cortical tissue-specific promotor, has facilitated the delivery of transgene in the motor cortex and affected especially the forelimb, rather than the hind limb motor functions.

This study is supported by TÜBİTAK (Grant #116S408).

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P085

PERINEURAL APPLICATION OF RESINIFERATOXIN ON UNINJURED L3 AND L4 NERVES COMPLETELY ALLEVIATES THERMAL AND MECHANICAL HYPERALGESIA FOLLOWING L5 NERVE INJURY IN RATS

Safa Shehab, Hayate Javed, Sumisha Rehmathulla, and Milos Ljubisavljevic

Department of Anatomy and Physiology, College of Medicine & Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates

s.shehab@uaeu.ac.ae

Aims: This study assessed the neuroanatomical organization of neuropathic pain processing in rat lumbar spinal cord. We examined whether perineural application of resiniferatoxin (RTX) to L4, or both L3 and L4 nerves, would completely eliminate neuropathic pain manifestations following L5 nerve injury.

Methods: Left L5 nerve was ligated and cut to induce neuropathic pain in the hind paw of adult Wistar rats. At the same time, the animals also had RTX (0.002%) or vehicle application for 30 min to either left L4, or to both L3 and L4 nerves. Thermal and mechanical hyperalgesia were estimated by measuring the threshold paw withdrawal latency (plantar and dynamic plantar aesthesiometer) before surgery and 3, 7, 14, 21 and 28 days postoperatively. Confocal and EM microscopy was used to determine RTX effects on the levels of TRPV1, CGRP and IB4 immunoreactivities and ultrastructural morphology of L4 nerve and DRG.

Results: RTX application on L4 nerve produced a significant reduction in the thermal and mechanical hyperalgesia ($p<0.01$; $p<0.001$). However, RTX application on both L3 and L4 nerves completely abolished thermal and mechanical hyperalgesia which showed no significant difference compared with right control paw ($p>0.05$). RTX induced marked down-regulation of TRPV1, CGRP, and IB4 immunoreactivities. There were no detectable ultrastructural changes in the treated nerves and L4 DRG.

Conclusions: The data demonstrate the role of the uninjured adjacent nerves in the maintenance and perpetuation of peripheral neuropathic pain. RTX application on both uninjured L3 and L4 nerves was crucial to completely abolish the neuropathic manifestations following L5 nerve injury.

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P086

USING A FRAGMENT-BASED APPROACH TO IDENTIFY NOVEL SERINE RACEMASE INHIBITORS FOR TREATMENT-RESISTANT DEPRESSION

Olivera Grubisha[1], Chloe Koulouris[2], Benjamin D Bax[1] and John Atack[1]

1Medicines Discovery Institute, Cardiff University, Park Place, Cardiff, United Kingdom;
2Sussex Drug Discovery Centre, University of Sussex, Falmer, Brighton, United Kingdom

grubishao@cardiff.ac.uk

Aims: Dysregulation of NMDA receptors has been implicated in the pathophysiology of many psychiatric and neurodegenerative diseases. Most recently, esketamine, an NMDA receptor antagonist, was approved by the FDA for treatment-resistant depression highlighting the therapeutic benefit in modulating NMDA receptor function in this condition. However, the drug carries safety risks that require careful administration, underscoring the need for improved therapies. One such strategy is to indirectly modulate NMDAR activity by targeting serine racemase (SR), an enzyme that generates NMDA receptor co-agonist D-serine. Here we take a fragment-based approach with the aim of identifying novel SR inhibitors.

Methods: A biochemical assay measuring SR enzyme activity was optimized and used to screen a fragment-based library of ~3000 compounds. Compounds were filtered using a flow-scheme of additional biochemical and biophysical assays and x-ray crystallography.

Results: 61 compounds from the screen inhibited SR with IC50 values < 1 mM. Direct binding was confirmed for 13 of these and the structure of 1 fragment (F01) bound to SR was obtained by x-ray crystallography at 1.8 Å resolution. The structure revealed that F01 binds in the orthosteric site and inhibits SR by preventing a ligand-induced conformational shift in the presence of substrate.

Conclusion: This novel series of SR orthosteric inhibitors form the basis for future structure-based optimisation and hit-to-lead development. Further improvements will produce a potent tool compound that will help dissect the role of SR in treatment-resistant depression and other CNS disorders.

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POSTER SESSION 1

P087

SEX-SPECIFIC HIPPOCAMPAL METABOLIC SIGNATURES AT THE ONSET OF SYSTEMIC INFLAMMATION WITH LIPOPOLYSACCHARIDE IN THE APPSWE/PS1DE9 MOUSE MODEL OF ALZHEIMER'S DISEASE

Alessandra Agostini[1], Ding Yuchun[2,3], Bai Li[3], David A. Kendall[1], Marie-Christine Pardon[1]

1School of Life Sciences, Division of Physiology, Pharmacology and Neuroscience, Medical School, Queens Medical Centre, Nottingham, NG7 2UH, UK;

2School of Computer Sciences, University of Nottingham, Jubilee Campus, Wollaton Road, Nottingham, NG8 1BB, UK ;

3Present address: School of Computing Science, Urban Sciences Building, Newcastle University, 1 Science Square, Science Central, Newcastle upon Tyne, NE4 5TG, UK

marie.pardon@nottingham.ac.uk

Aims: Systemic inflammation enhances the progression of Alzheimer's disease (AD). Lipopolysaccharide (LPS) is a potent pro-inflammatory endotoxin *produced by the gut, found in excess levels in AD where it associates with neurological hallmarks of pathology. Sex differences in susceptibility to inflammation and AD progression have been reported, but how this impact LPS responses remains under investigated.* We aimed here to comprehensively identify hippocampal metabolic processes occurring at onset of systemic inflammation at an early pathological stage, and investigated the sexual dimorphism in this response.

Methods: 4.5-month-old male and female APPswe/PS1dE9 mice were administered LPS *(100µg/kg, i.v.)* or PBS. LPS-induced sickness was assessed in the food burrowing and spontaneous alternation test, and by recording rectal temperature, 4 hours after inoculation. Blood and brains were collected to quantify hippocampal metabolites levels using LC-MS, circulating cytokine levels, and for immunostaining of microglia and astrocytes.

Results: *LPS induced comparable behavioural sickness responses and activation of both the serotonin and kynurenine pathways of tryptophan metabolism in the hippocampus of male and female wild-type and APP/PS1 mice. Males also exhibited a greater temperature response to LPS associated with a pro-inflammatory-like downregulation of pyruvate metabolism and methionine metabolism whereas females showed a greater cytokine response and anti-inflammatory-like downregulation of hippocampal methylglyoxal and methionine metabolism. Metabolic changes were not associated with morphological markers of immune cell activation.*

Conclusions: Both pro- and anti-inflammatory metabolic pathways were simultaneously recruited in the hippocampus with a more pronounced anti-inflammatory component in females, suggesting that they are more tolerant to acute *systemic inflammation*.

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P088

NIGRAL DOPAMINE RELEASE GATES MOTOR ACTIVITY IN A NOVEL MOUSE MODEL OF PROGRESSIVE PARKINSONISM

Gonzalez-Rodriguez P[1], Zampese E[1], Stout KA[1], Ilijic E[1], Guzman J[1], Lopez-Barneo J[3], Schumacker PT[2], Surmeier DJ[1]

1Department of Physiology, Feinberg School of Medicine, Northwestern University, Chicago, IL, United States, 2Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, IL, United States, 3Department of Physiology, Institute of Biomedicine of Seville, University of Seville, Seville, Spain

p-gonzalezrodriguez@northwestern.edu

Degeneration of substantia nigra dopaminergic-(SN-DA) neurons is responsible for the cardinal motor symptoms of PD. Several lines of evidence suggest that this loss is attributable to a deficit in mitochondrial complex I-(MCI) function. To test this hypothesis, a critical subunit of MCI-(Ndufs2) was conditionally deleted in DA neurons.

At weaning, mice lacking Ndufs2 in DA neurons were normal in appearance and motor behavior. However, by P20, electron transport chain-(ETC) function in SN-DA neurons was insufficient to support mitochondrial membrane potential and mitochondria began to import ATP from the cytosol to run complex V in reverse. Cytosolic ATP levels at this point were maintained solely by glycolysis. By P40, striatal DA release plummeted to unmeasurable levels and striatal tyrosine hydroxylase immunoreactivity-(TH-IR) was lost; this was accompanied by motor learning and sequencing deficits, but not parkinsonian motor deficits. Subsequently, by P60, these mice developed a progressive and severe, levodopa-responsive parkinsonian phenotype. This phenotype was correlated with loss of SN-DA release and down-regulation of TH-IR in the SN, but not frank loss of neurons. To test the hypothesis, aromatic acid decarboxylase-(AADC) construct was stereotaxically injected into the SN and the response to levodopa measured. The motor benefit of levodopa was enhanced.

Hence, these studies show that loss of MCI function induces an axon-first, staged loss of SN-DA neuron function, mimicking the staging of pathology in PD patients. Moreover, these studies also suggest that contrary to current models, loss of SN-DA release –not striatal release– is critical for the emergence of parkinsonian motor symptoms.

This work was supported by the JPB Foundation (DJS) a Flanagan/Alfonso Martin Escudero Fellowship (PGR) and NINDS NS047085 (DJS).

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P089

BENFOTIAMINE, A SYNTHETIC ANALOGUE OF B1 VITAMIN, IMPROVES HYPOTHALAMIC INSULIN SIGNALING AND METABOLIC PARAMETERS ASSOCIATED WITH STZ-ICV MODEL OF ALZHEIMER'S DISEASE

Moraes R.C.M.[1,2], Gonçalves A.C.[3], Portari G.V., Lima G.C.A.[1], Kleinridders A.[2], Torrão A.S.[1]

1Laboratory of Neuronal Communication, Department of Physiology and Biophysics, Institute of Biomedical Sciences – University of Sao Paulo (ICB-USP), Sao Paulo – Brazil;
2Central Regulation of Metabolism Research Group, German Institute of Human Nutrition Potsdam-Rehbrüecke (DIfE), Nuthetall – Germany;
3Laboratory of Experimental Nutrition, Department of Nutrition – Federal University of Triangulo Mineiro (UFTM), Uberaba – Brazil

moraes.ruan@usp.br

Alzheimer's disease (AD) patients also suffer from metabolic disorders, including weight loss. The hypothalamus presents neurodegeneration in AD patients, and AD-affected brains display insulin resistance. Vitamin B1 is decreased in patients with AD. Our objective was to evaluate the effects of benfotiamine (BFT) in the intracerebroventricular streptozotocin (ICV-STZ) AD model. Metabolism, insulin signaling, inflammation and apoptosis were studied.

Rats submitted to ICV-STZ were 30-days supplemented with 150mg/kg BFT divided in CTL, CTLB, STZ, and STZB. Food intake was measured and after supplementation, blood was collected, visceral adipose tissue weight determined and hypothalamic samples were used for immunoblotting. In addition, hypothalamic cells (CLU183) were stimulated with STZ and/or BFT and cell toxicity and insulin sensitivity were evaluated.

BFT treatment increased blood thiamine and thiamine transporters in hypothalamus of STZB rats. STZ reduced body weight but not food intake and caused lipoatrophy, whereas BFT protected against these dysregulations. Hypothalamic GFAP was increased in STZ rats, suggesting inflammation, unaffected by BFT treatment. Changes in insulin signaling resulted in higher phosphorylation of ERK1/2, reversed by BFT. Further STZ treatment decreased BCL-2/BAX ratio indicating apoptosis, which was normalized in STZB rats. On CLU183 neurons, STZ did not result in insulin resistance, but benfotiamine increased insulin sensitivity in cells exposed to STZ, resulting in enhanced cell survival.

ICV-STZ causes hypothalamic changes that provoke an energy imbalance resulting in weight loss and lipoatrophy. BFT partially protects against these alterations, modulating insulin sensitivity and apoptosis, preventing neuronal death and reversing weight and fat loss.

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P090

LATERAL DIFFERENCE AND SEX DIFFERENCE IN ELECTROPHYSIOLOGICAL PROPERTIES OF HVCX NEURONS IN ADULT ZEBRA FINCHES

Feng Kai, Li Dongfeng

School of Life Science, South China Normal University, Guangzhou 510631, China

dfliswx@126.com

In this experiment, we investigate the electrophysiological properties of HVCX neurons in order to explore whether there are lateral and sex differences in HVCX neurons in adult female and male zebra finches.

The HVCX neurons were given 5ms, 300pA and 500ms, 100pA stimulation to induce action potentials and their electrophysiological properties were statistically analyzed.

The results showed that there was no lateral difference in the electrophysiological properties of HVCX neurons in the left and right brain of female birds, but the latency of action potential and the AHP time to peak in the right brain of male birds were significantly lower than those in the left brain, and the spike rate was higher than that in the left brain. There was no significant difference in electrophysiological properties of HVCX neurons in the left brain between male and female birds. The latency of action potential and the AHP time to peak in the right brain of male birds were significantly lower than female birds, and the spike rate of the right brain of male birds was significantly higher than female birds.

The results showed that the excitability of HVCX neurons on the right side of the male was higher than that on the left brain. There is sex difference in electrophysiological properties of right HVCX neurons between male and female zebra finches.

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P91

EXCESSIVE LINKING OF HIPPOCAMPAL MEMORY REPRESENTATIONS IN A RAT MODEL OF SCHIZOPHRENIA AND THE EFFECT OF ADOLESCENT COGNITIVE TRAINING

Branislav Krajcovic[1,2], Hana Brozka[1], Helena Buchtova[1], Ales Stuchlik[1], Stepan Kubik[1]

1Department of Neurophysiology of Memory, Institute of Physiology, Czech Academy of Sciences, Prague, Czech Republic;
23rd Faculty of Medicine, Charles University, Prague, Czech Republic

branislav.krajcovic@fgu.cas.cz

Aims: Memories acquired in close temporal proximity are often recalled in sequence where activation of one memory primes recall of a related memory. Ensembles of hippocampal (HPC) neurons form the basis of memory acquisition, storage and recall, i.e. represent a memory trace. Overlap of neuronal ensembles is considered to be the mechanism underlying linking of different memories, so that activation of one memory trace/ensemble primes the re-activation of another, partially overlapping ensemble. Schizophrenia (SZ) patients display excessive associations in thought and speech. We propose that excessive overlap of neuronal ensembles representing distinct behavioral experiences forms the basis of hyperassociations. In addition, cognitive training could be protective by attenuating the excessive ensemble linking.

Methods: Long Evans rats received 5 days of cognitive training during adolescence (PD50-55) in form of active place avoidance on a continuously rotating arena (Carousel task) or were merely handeled. Since the arena- and room-frames of reference were dissociated in the Carousel task and because only room-bound cues were relevant for successful avoidance, the cognitve control processes were engaged to resolve the conflict between relevant and irrelevant stimulus dimensions. In adulthood (PD90+), rats were treated with an NMDAR antagonist MK-801 (0.15 mg/kg i.p.) and explored either the same novel environment twice (A/A) or visited two different novel environments (A/B). Analysis of immediate-early gene expression (Arc/Homer1a catFISH) was used to determine HPC CA1 ensembles active during the two exploratory episodes and to assess degree of the their overlap.

Results: Our preliminary results show that: 1) In saline-treated animals, irrespective of cognitive training, the A/A ensemble overlap was significantly higher than in the A/B condition. 2) In the untrained MK-801 rats, the ensemble overlap in A/B condition was not significantly different from A/A. 3) In MK-801 animals that explored A/B, a trend toward decrease in ensemble overlap was observed in cognitively trained animals compared to untrained rats. However, this difference was not statistically significant due to high variance.

Conclusions: Our data support the notion of increased linking of HPC CA1 ensembles representing distinct behavioral experiences in a rat model of SZ. This observation is a replication of our previous study, lending robustness to this finding. Moreover, our preliminary data suggest that cognitive training during adolescence may ameliorate excessive ensemble linking – however, to conclusively evaluate this interpretation, additional experimental data is needed to compensate for high variance. In addition, more intensive cognitive training might have been preferable to deem the potential effect size larger and more consistent across animals.

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P092

ENHANCED EXPRESSION AND FUNCTION OF P2X2 RECEPTOR IN SUPRAOPTIC NEURONS AFTER STIMULATION THROUGH REFEEDING AFTER FASTING

Milorad Ivetic[1,2], Anirban Bhattacharya[1] and Hana Zemkova[1]

1Institute of Physiology, Czech Academy of Sciences;
2Faculty of Science, Charles University;
Prague, Czech Republic

milorad.ivetic@fgu.cas.cz

Aims: Magnocellular neurons in the supraoptic nucleus (SON) synthesizing and releasing arginine vasopressin (AVP) and oxytocin (OT) express ATP-stimulated purinergic P2X and P2Y receptors that modulate neurotransmitter release, but physiological role is unknown. Here, we tested a hypothesis that P2X receptors might play a role in release of hormones from SON neurons osmotically stimulated through refeeding after fasting.

Methods: We measured expression levels of mRNAs for the AVP, OT, and P2X2, P2X4, P2X7, P2Y1 and P2Y2 receptor genes in SON tissue from normally fed 30-day-old Wistar rats and rats refed for 2 h after 48 h of starvation. ATP-induced currents and spontaneous inhibitory postsynaptic currents (sIPSCs) were recorded from SON neurons in slices using standard whole-cell patch clamp technique.

Results: Quantitative real-time PCR revealed that the expression of P2X2 and AVP) mRNA was upregulated. P2X4, P2X7, P2Y2 and OT mRNA levels were not significantly changed and P2Y1 mRNA expression was decreased. Whole-cell patch clamp recording from presumable AVP neurons revealed that the amplitude of the ATP-stimulated somatic current and the incidence of ATP-induced sIPSCs frequency increases were significantly higher in fasted/refed rats than in controls. No evidence was found for changes in the presynaptic effect of ATP in presumable OT neurons not expressing somatic P2X receptors.

Conclusions: These results suggest that the increased synthesizes and release of AVP from SON neurons osmotically stimulated through refeeding after fasting is associated with enhanced expression and function of P2X2 receptor. This might lead to increased interactions between P2XR-expressing AVP neurons and their synchronization.

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P093

TRAP METHOD: A NEW APPROACH TO COMPARE THE NEURONS ACTIVATED DURING WAKING AND PARADOXICAL (REM) SLEEP

Risa Yamazaki, Dianru Wang, Anna De Laet, Hyunsook Lee, Sébastien Arthaud, Paul-Antoine Libourel, Patrice Fort, Pierre-Hervé Luppi

Team "SLEEP" UMR 5292 CNRS/U1028 INSERM, Centre de Recherche en Neurosciences de Lyon (CRNL), Lyon, France

risa.yamazaki@univ-lyon1.fr

Aims: We and others previously identified subcortical structures generating waking (W) and paradoxical (REM) sleep (PS) such as the sublaterodorsal tegmental nucleus (SLD) and supramammillary nucleus (SuM). We further recently showed that only a few limbic cortical structures including the dentate gyrus (DG) and the claustrum (CLA) are activated during PS in contrast to W in rats. Our aim is now to determine whether the same or different neurons are activated during PS and W and during two successive W and PS periods.

Methods: We set up a new genetic TRAP method combining DsRed expression under Fos promoter with Fos immunohistochemistry. We examined 3 mice groups: W-W (2h in open field), PSR-PSR (2h PS recovery after 48h PS deprivation) and W-PSR. All mice received 4-OHT 2h after the first condition and were perfused 2h after the second condition.

Results: In W-W group, a high percentage of DsRed neurons are Fos+ (double-labeled) in all regions examined excepting in the DG. In PSR-PSR, many double-labeled neurons were observed in SLD, LHA and SuM, a small number in the CLA and none in the DG. In W-PSR group, only a few double-labeled neurons were double-stained.

Conclusions: First, our results validate the TRAP method. They further indicate that W and PS are completely different states during which different populations of neurons are activated across time in cortical structures involved in cognition. Further, they open the avenue to the identification of the function of PS by means of manipulating their activity.

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P094

A ROLE FOR ASTROCYTES IN FRAGILE X SYNDROME?

Bataveljic D. [1], Pivonkova H. [2], Ezan P. [1], Menuet A. [3], Rouach N. [1]

1Center for Interdisciplinary Research in Biology, Collège de France, CNRS UMR 7241, INSERM U1050, Labex Memolife, PSL Research University, Paris, France;
2 Wellcome - MRC Cambridge Stem Cell Institute, University of Cambridge, Cambridge, UK;
3 UMR7355, Immunologie et Neurogénétique Expérimentales et Moléculaires (INEM), Centre National de la Recherche Scientifique, Orléans, France

danijela.bataveljic@college-de-france.fr

Aims: Fragile X syndrome (FXS) is a common inherited form of intellectual disability that is associated with cognitive and behavioral impairment and high incidence of seizures. Recent studies demonstrated the involvement of several K+ channels in pathology of FXS, suggesting alteration in K+ homeostasis in the disease. Astrocytes control K+ homeostasis and neuronal excitability by efficient removal of excessive K+ released during synaptic activity. The aim of our study was to explore a role for astrocytes in disturbed K+ homeostasis in FXS.

Methods: The experiments were performed in acute hippocampal slices of WT and Fmr1 KO mice. Whole-cell patch-clamp recordings were performed to describe: 1) intrinsic properties of CA1 neurons and 2) synaptically-evoked astrocyte potassium current. Ion-sensitive electrodes were used to measure extracellular K+ concentration ([K+]o).

Results: Our data demonstrated increased excitability of CA1 pyramidal neurons in Fmr1 KO mice. Furthermore we showed that neuronal hyperexcitability is associated with increase of [K+]o transient and undershoot in Fmr1 KO hippocampal slices. Our results reveal significantly reduced synaptically-evoked astrocyte potassium current in Fmr1 KO mice suggesting that impaired K+ homeostasis results from reduced astroglial uptake of K+.

Conclusions: In this study we demonstrated reduced ability of Fmr1 KO astrocytes to uptake extracellular K+ during synaptic activity. Our data provide the first evidence indicating a role for astrocytes in the alteration of extracellular K+ homeostasis in FXS.

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P095

EARLY MANIPULATION OF INTRINSIC PLASTICITY OF CORTICAL ENGRAM CELLS IMPACTS MEMORY PRECISION OF CONSOLIDATED MEMORY

Senka Hadzibegovic[1,2], Liangying Zhu[1,3], Isabel Del Pino[1,3], Katy Le Corf[3], Melanie Ginger[3], Oliver Nicole[1,2], Bruno Bontempi[1,2,4], Andreas Frick[1,3,4]

1Université de Bordeaux, Bordeaux, France, 2UMR 5293, CNRS, Institut des Maladies Neurodégénératives, Bordeaux, France, 3INSERM U1215, Neurocentre Magendie, Bordeaux, France, 4These authors jointly supervised this work

senka.hadzibegovic@u-bordeaux.fr

Aims: The anterior cingulate cortex (ACC) is thought to play a critical role in remote contextual fear memory formation and retrieval. Upon encoding, neurons undergo early tagging to ensure the progressive hippocampal-driven rewiring of cortical networks that support storage of enduring memories. Yet, identity and organization of the neuronal ensembles within the ACC, which hold engrams for particular memory events, are not known. We designed experiments to investigate whether early manipulation of intrinsic excitability of cortical engram cells could affect the content of remote memories once consolidated.

Methods: We used a tet-tag mouse line which enabled us to target and manipulate only the neurons activated during memory encoding by expressing modified muscarinic hM4D/hM3Dq receptors under control of the tetracycline-regulated promoter. Thus, these engineered receptors were expressed specifically in ACC neurons engaged in a context-discrimination protocol and their excitability was modulated by injections of the receptor ligand clozapine-N-oxide.

Results: Our data show that ACC is strongly recruited during encoding and formation of contextual fear memories. Decreasing, after encoding, the excitability of the engram cells involved in initial tagging of contextual fear memory improved the precision of remote memory by enabling mice to better discriminate fearful and unfearful contexts. In contrast, increasing excitability of these neurons reduced remote memory precision as revealed by a decline in context discrimination.

Conclusion: Early manipulation of intrinsic excitability of engram cells can impact the maturation of remote memories by altering their content over time and offers a new therapeutic opportunity to protect memory in neurodegenerative diseases.

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P096

ROLE OF OREXINS IN THE DETERMINATION OF SLEEP PATTERNS ACCOMPANYING TORPOR

Lo Martire V.[1], Alvente S.[1], Amici R.[1], Bastianini S.[1], Berteotti C.[1], Cerri M.[1], Silvani A.[1], Swoap S.[2], Zoccoli G.[1]

1 Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum-University of Bologna, Bologna, Italy;
2 Department of Biology, Williams College, Williamstown, Massachusetts, United States

Aims: Under conditions of scarce food availability and low ambient temperature, mouse rapidly enters into torpor, a state of transient metabolic suppression, characterized by the controlled lowering of metabolic rate, body temperature, and physical activity. This condition of hypometabolism is similar to that present during sleep. Orexin neuropeptides control sleep, body temperature, and food intake. The role of orexins in the relationship between torpor and sleep is still unclear. We investigated whether orexin deficiency entails sleep alterations during torpor in mice.

Methods: female orexin knock-out mice (KO, n = 6) and congenic wild-type controls (WT, n = 5) were implanted with a thermistor to measure brain temperature (BT), and electroencephalographic (EEG) and electromyographic (EMG) electrodes to discriminate wake-sleep states. Biosignals were recorded in calorically restricted mice exposed to an ambient temperature of 20°C. Sleep was scored manually on 4-s epochs based on EEG and EMG signals. An episode of torpor included a phase of deep torpor (time period during which BT was stable and the absolute value was ≤25°C) preceded by a phase during which BT monotonically decreased resulting in an overall BT reduction ≥ 5 °C (cooling) and followed by a phase during which BT monotonically increased resulting in an overall BT increase ≥ 5 °C up to the normal value (rewarming). Wake-sleep pattern during each phase of torpor episodes was compared between KO and WT mice (ANOVA, significance $p < 0.05$).

Results: the percentage of recording periods spent in each wake-sleep state did not significantly differ between KO and WT mice in none of the phases accompanying torpor.

Conclusions: orexins have not a role in the determination of sleep patterns accompanying the different phases of torpor in mice. The knowledge of mechanisms underlying torpor may open the way to induction of synthetic torpor-like states in humans for medical application and long-term space travel.

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P097

ULTRAFAST OPTOGENETIC STIMULATION OF THE AUDITORY PATHWAY BY TARGETING-OPTIMIZED CHRONOS

Vladan Rankovic[1,2], Daniel Keppeler[1,3], Burak Bali[1,2,3], David Lopez de la Morena[1,3,4], Antoine Huet[1,4], Tobias Moser[1,3,4,5]

1Institute for Auditory Neuroscience and InnerEarLab, University Medical Center Göttingen, Göttingen, Germany;

2Restorative Cochlear Genomics Group, German Primate Center, Göttingen, Germany;

3Göttingen Graduate School for Neurosciences and Molecular Biosciences, University of Göttingen, Göttingen, Germany;

4Auditory Neuroscience and Optogenetics Laboratory, German Primate Center, Göttingen, Germany;

5Max Planck Institute for Experimental Medicine, Göttingen, Germany

vrankovic@dpz.eu

Optogenetic stimulation of spiral ganglion neurons (SGNs) in the ear provides a future alternative to electrical stimulation used in cochlear implants. As light can be conveniently confined in space, optical stimulation promises to increase the number of independent stimulation channels. However, most channelrhodopsins do not support the high temporal fidelity pertinent to auditory coding because they require milliseconds to close after light-off. The opsin Chronos could overcome this main limitation by ultrafast closing kinetics (Klapoetke et al., 2014).

Using a viral approach for in vivo transduction of SGNs, we successfully expressed Chronos in mice and gerbils. In order to enhance Chronos expression at the plasma membrane, we improved its trafficking to the plasma membrane (Chronos-ES/TS). Following efficient transduction of SGNs using early postnatal injection of the adeno-associated virus AAV-PHP.B into rodent cochlea, fiber-based optical stimulation elicited optical auditory brainstem responses (oABR) with minimal latencies of 1 ms, thresholds of 5 µJ and 100 µs per pulse, and sizable amplitudes even at 1000 Hz of stimulation.

Recordings from single SGNs demonstrated high temporal fidelity of light-evoked spiking. To conclude, efficient virus-mediated expression of targeting-optimized Chronos-ES/TS achieves ultrafast optogenetic control of neurons.

Klapoetke, N.C., Murata, Y., Kim, S.S., Pulver, S.R., Birdsey-Benson, A., Cho, Y.K., Morimoto, T.K., Chuong, A.S., Carpenter, E.J., Tian, Z., et al. (2014). Independent optical excitation of distinct neural populations. Nat. Methods 11, 338–346.

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P098

ACTIVITY OF BASAL FOREBRAIN NEURONS IN A CLASSICAL SUSTAINED ATTENTION TASK

Diana Balazsfi[1], Eszter Birtalan[4], Balint Kiraly[1,2,3], Ildiko Horvath[2,5], Domokos Mathe[2,5], Krisztian Szigeti[2,5], Joshua I. Sanders[6,7], Balazs Hangya[1]

1Lendület Laboratory of Systems Neuroscience, Department of Cellular and Network Neurobiology, Institute of Experimental Medicine – Hungarian Academy of Sciences, Budapest, Hungary;
2Department of Biophysics and Radiation Biology, Semmelweis University, Budapest, Hungary;
3Department of Biological Physics, Eötvös Loránd University, Budapest, Hungary;
4Eötvös Lorand University, Faculty of Science Institute of Biology, Budapest, Hungary;
5CROmed Translational Research Centers, Budapest, Hungary;
6Cold Spring Harbor Laboratory, Cold Spring Harbor, USA;
7The Danish Research Institute of Translational Neuroscience, Aarhus University, Aarhus, Denmark

balazsfi.diana@koki.mta.hu

The basal forebrain (BF) plays key roles in multiple brain functions, including sleep-wake regulation, attention and learning/memory. The BF consists of cholinergic, GABAergic, and glutamatergic neurons. Stimulation of BF cholinergic neurons enhances visual attention performance including the detection of sensory cues, in which projections from the horizontal diagonal band of Broca (HDB) to the prefrontal cortex are especially important. Less is known about potential involvement of BF GABAergic and glutamatergic neurons in attention.

To test whether neurons of the HDB show activity patterns correlated with attention, we trained mice on the 5-choice serial reaction time task (5-CSRTT), which measures the ability of rodents to sustain spatial attention. We developed an automated training system, in which mice freely alternated between their home cage and a training cage. To investigate the firing patterns of HDB neurons, we implanted tetrodes to the mouse HDB. To verify the placement of the implants immediately after the surgery we combined CT and MRI scans.

We found that the automated training greatly improved learning speed. Recorded neurons were clustered based on their firing rate changes during the behaviour test. A number of neurons -also optogenetically tagged cholinergic cells- in the HDB responded phasically to light cues but decreased their firing rates during rewarded trials. Firing rate changes in the 'attention period' preceding cue presentation were less frequent.

These data indicate that HDB neurons may have a more distinct role in learning; however, a specific role of cholinergic cells in sustained attention is yet to be tested.

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P099

IN VIVO MODEL OF THE AGING BLOOD-BRAIN BARRIER: OBSERVATIONS OF THE FUNCTIONAL AND STRUCTURAL CHANGES WITH MULTIPLE METHODS

Bors L[1], Bajza Á[1], Tóth K[2], Csorba A[3], Máthé D[4], Szigeti K[4], Gyertyán I[5] and Erdő F[1]

[1]Pázmány Péter Catholic University, Faculty of Information Technology and Bionics, Budapest, [2]MTA-TTK Institute of Cognitive Neuroscience and Psychology, Budapest, [3]University of Szeged, Faculty of Pharmacy, Deparment of Pharmacognosy, Szeged, [4]Semmelweis University, Faculty of Medicine, Department of Biophysics and Radiation Biology, Budapest,[5]Semmelweis University, Department of Pharmacology and Pharmacotherapy, Budapest

lucaannabors@outlook.com

Aim: Our study aimed to compare the structure of brain microvessels and function of P-glycoprotein (P-gp) at the BBB and its behavioral consequences in young and aged rats.

Methods: In our study young and aging male Wistar rats were used. Comparative magnetic resonance imaging (MRI) and electronmicroscopy were performed to observe anatomical changes. The function of P-gp were investigated with dual and triple-probe microdialysis techniques with the use of P-gp substrate, quinidine in presence and absence of a P-gp inhibitor, PSC-833. The samples were analyzed with LCMS-MS. Single photon emission computed tomography (SPECT) imaging was also applied to compare P-gp functionality. The expression of some BBB proteins (efflux transporters, claudin-5, GFAP) were also investigated. For behavioral analysis Morris-Water maze and New Object Recognition tests were performed.

Results: In the control groups aged rats had higher levels of QND in brain than in young rats. Results of P-gp inhibition suggesting lower expression or decreased functionality of P-gp. With MR imaging and electronmicroscopic images of the BBB multiple structural changes were found. The expression of BBB proteins were altered. However, there was no significant cognitive impairment observed with healthy aging in the behavioral tests.

Conclusions: Our results indicate that the BBB permeability and structure changes during aging. This can be the consequence of a lower expression and/or reduced P-gp function and the morphological alterations of the brain capillaries and the associated cell structures with aging but, on the other hand, there was no memory and learning deficit observed in aged subjects.

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P100

PRESYNAPTIC PROPERTIES OF THE MORPHO-FUNCTIONALLY DIVERSE AXON TERMINALS OF HIPPOCAMPAL MOSSY FIBERS

János Brunner, Endre Levente Marosi, János Szabadics

Institute of Experimental Medicine, Hungarian Academy of Sciences, Hungary

brunnerj@koki.hu

Aims: Axon terminals of hippocampal mossy fibers (MFs) are structurally and functionally heterogeneous. Large mossy fiber boutons (LMFBs) make synapses with pyramidal cells in the CA3 region and with mossy cells in the hilar region of the dentate gyrus. Each LMFB forms tens of release-sites onto single target cells which are characterized with low release probability. In contrast to these unusually large boutons, most MF terminals are much smaller, similarly to typical cortical axons. Small mossy fiber boutons (sMFBs) excite only GABAergic cells usually with higher release probability. Thus, comparison of LMFBs in the CA3 and in the hilus and sMFBs provides ideal experimental conditions to address the theoretically important questions whether target-, size- and morphology-dependent action potential- and presynaptic calcium-signaling support functional diversity within the same axon? How good models are the unusually large boutons for general signaling rules in typical axons?

Methods: Direct patch clamp recordings from sMFBs, LMFBs and axonal shafts in acute slices.

Results: Action potential shapes and their short-term dynamics were surprisingly similar in all MF axonal structures regardless of their different functions. Furthermore, outside-out patch recordings revealed that all of them (including axonal shafts) have substantial amount of sodium and potassium currents, which would support local regulation of the firing properties. Pharmacological analysis of isolated calcium currents in LMFBs in the hilus and CA3 regions showed similar involvement of N- and P/Q-type channels.

Conclusions: Action potential signaling and the related calcium mechanisms are surprisingly uniform among the functionally different axonal structures of MFs.

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P101

DENDRITIC ACTIVITIES IN PYRAMIDAL CELLS DURING SHARP WAVE-RIPPLE OSCILLATIONS

Balázs Chiovini[1,2], Dénes Pálfi[1,2], Gábor Juhász[1,2], Linda Judák[1], Zsolt Mezriczky[2], Anna Mihály[2], Gergely Katona[1,2], Balázs Rózsa[1,2]

1Institute of Experimental Medicine, Hungarian Academy of Sciences, 3D Functional Network and Dendritic Imaging, Budapest, Hungary; 2Pázmány Péter Catholic University, Faculty of Information Technology and Bionics, Two-photon Laboratory, Budapest, Hungary

chiovini.balazs@koki.hu

Aims: Hippocampal sharp wave-ripple (SPW-R) complexes have crucial role in memory formation and consolidation. SPW-Rs are driven by interactions between excitatory pyramidal cells and inhibitory interneurons. In our previous work, we have shown dendritic regenerative activities in fast spiking parvalbumin containing interneurons in vitro and later in vivo. Although the dendritic integration mechanisms of functionally working hippocampal pyramidal neurons remain elusive.

Methods: Because of technical and methodical problems the relationship between SPWs, field ripple oscillations and dendritic Ca2+ events have not yet been studied in pyramidal neurons. In our measurements we combined two-photon random-access point scanning imaging and uncaging techniques with electrophysiological recordings and pharmacology.

Results: Beside the field potential recordings we were able to measure simultaneously the activity patterns of principal cell dendritic signal integration mechanisms in vitro and in vivo. We showed complex and regenerative Ca2+ events at different subcellular regions of pyramidal cells. Moreover, we showed the dependence of these regenerative events on voltage-gated Ca2+ channels in spiny dendrites of principal neurons in vitro.

Conclusions: We were able to record hippocampal principal cell activity patterns during SPW-Rs along their dendrites not only in vitro but in vivo as well. The dendritic Ca2+ events showed non-uniform appearance in principal cells just like in our previously published interneurons. With these results it is possible to better understand the mechanisms of complex hippocampal coincidence detection and neuronal functions during input-output formation and conversion in vitro and in vivo.

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P102

QUASI-SIMULTANEOUS IN VIVO PHOTOSIMULATION AND CALCIUM IMAGING WITH MULTI-3D ACOUSTO-OPTICAL TWO-PHOTON MICROSCOPY

Csaba Csupernyák, Máté Marosi, Gergely Szalay, Gergely Katona, Katalin Ócsai, Róbert Bolla, András Fehér, Máté Veress, Áron Szepesi, Balázs Rózsa

Institute of Experimental Medicine Hungarian Academy of Sciences, Budapest, Hungary

csaba.csupernyak@femtonics.eu

Aims: The major direction of developments in two-photon microscopy is to exploit the widening toolset of optogenetics to allow simultaneous stimulation and imaging in 3D which is an excellent approach to further understand mechanisms in the living brain. Efficacy of two-photon optogenetics is usually limited by single focus stimulation. We sought to overrun this limitation using cutting-edge quasi-simultaneous two-photon photostimulation and Ca2+-imaging.

Methods: We used a novel acousto-optical scanning solution which is controlling two laser lines with different wavelengths in three dimensions. Switching between the two lasers and scanning patterns happens almost instantaneously, making it possible to perform photostimulation and Ca2+-imaging in an interleaved fashion. We used Thy1-Cre mouse line expressing soma-targeted ChrimsonR-mRuby2 and GCaMP6f.

Results: By fine-tuning the scanning parameters, we were able to record every second frame for imaging during stimulation, which let us follow activity even during photostimulation. With this technique it is possible to affect and monitor at least 80 neurons in a desired 3D network. As a result, since interlaminar connection is a crucial feature of cortical processing, with this method we can select, image and stimulate neuronal ensembles in a more sophisticated way than with conventional methods, taking us closer to dynamic cortical connection mapping and understanding of the main features of information processing.

Conclusions: We showed for the first time that it is possible to use acousto-optical focusing to perform quasi-simultaneous imaging and photostimulation of a desired neural network in large cortical volume with micrometer resolution.

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P103

IMPACT OF THE RECORDING SITE LOCATION ON THE RECORDING PERFORMANCE OF SILICON PROBES IN ACUTE EXPERIMENTS

Richárd Fiáth[1,2], Domokos Meszéna[1,2], István Ulbert[1,2]

1Faculty of Information Technology and Bionics, Pázmány Péter Catholic University, H-1083 Budapest, Hungary;
2Institute of Cognitive Neuroscience and Psychology, Research Centre for Natural Sciences, Hungarian Academy of Sciences, H-1117 Budapest, Hungary

fiath.richard@gmail.com

Aims: Multisite, silicon-based probes are widely used tools to record the electrical activity of neuronal populations. Several physical attributes of these devices (e.g. shaft thickness, tip geometry) are designed to improve the quality of the recorded brain signals by decreasing the damage done to the brain tissue. Here, our goal was to investigate whether the location of recording sites on the silicon shaft might affect the recording performance obtained in acute experiments.

Methods: High-density, single-shank, 128-site silicon probes having a shaft cross-section of 50 × 100 µm2 (thickness × width) and a recording site area of 20 × 20 µm2 were acutely implanted into the neocortex of ketamine/xylazine anesthetized rats (n = 9), then wideband (0.1 – 7500 Hz) activity was recorded. After the experiments, various quantitative properties (e.g. single-unit yield, peak-to-peak amplitude of single unit spikes, signal-to-noise ratio) of the recorded cortical activity were compared between sites located on the edge or the center of the probe.

Results: Based on our preliminary results, both the signal-to-noise ratio and the number of separable single units were similar between the two site locations. However, the peak-to-peak amplitude of spikes of neurons isolated on edge sites were significantly higher compared to spike amplitudes measured on center sites.

Conclusions: With the shaft width used in this study, the recording performance was only slightly better on the edge sites compared to center sites. The higher spike amplitudes measured on edge sites might be the result of less tissue damage near the edge of the probe.

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P104

THE ROLE OF PARVALBUMIN POSITIVE BASAL FOREBRAIN NEURONS IN CODING SURPRISE AND VALENCE DURING PAVLOVIAN CONDITIONING

Panna Hegedus, Julia Heckenast, Balazs Hangya

Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary

hegedus.panna@koki.mta.hu

Aims: GABAergic neurons of the basal forebrain (BF) display activation proportional to behavioral salience. Therefore, it is possible that the BF may be involved in broadcasting signals related to outcome expectations during reinforcement learning. The main goal of our experiment is to reveal the function of parvalbumin (PV) positive BF neurons in reinforcement learning.

Methods: To test this hypothesis, we trained mice on an auditory pavlovian task, in which two different tones predicted likely reward or punishment. Next, we recorded and optogenetically identified PV-positive GABAergic neurons from the horizontal limb of the diagonal band of Broca, HDB while mice were performing the task. To reveal the possible projections of the PV-HDB neurons, we performed anterograde tracing and used immunohistochemistry to identify the possible cell types of different areas targeted by this projection.

Results: Identified PV positive neurons were responding by phasic activation to punishment but not to reward during the task. With a tendency to respond with stronger activation to surprising punishment. Furthermore, higher frequency of anticipatory licking predicted stronger responses of PV neurons to punishment. Mapping the projections of HDB PV-neurons revealed that they may serve as a major input to the limbic navigation system.

Conclusion: Here we examined the function of a less known GABAergic projection system arising from the BF in reinforcement learning and we have found that it can transmit negative valence and surprise value to subcortical targets, mostly to the limbic navigation system. This projection can be crucial in context dependent learning of aversive stimuli.

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P105

HETEROGENEOUS SPINDLE- AND THETA- PHASE PREFERENCE OF SUPRAGRANULAR REGULAR SPIKING INTERNEURONS DURING NON-REM AND REM SLEEP

Horváth J, Averkin RG, Bordé S, Dashkovskyi V, Szemenyei V, Tamás G

MTA-SZTE Research Group for Cortical Microcircuits, Department of Physiology, Anatomy and Neuroscience, University of Szeged, Szeged, Hungary

horvath.janos3@gmail.com

Aims: Neocortical fast-spiking interneurons (FSIs) show spatiotemporally structured firing relative to rhythmic population activity during non-REM sleep, but our understanding of the activity of regular spiking interneurons (RSIs) is less clear.

Methods: We applied a drug free installation of a pipette microdrive assembly for juxtacellular recording and labelling of supragranular RSIs in the parietal cortex during natural sleep and wakefulness in Wistar rats.

Results: Action potentials of RSIs were wider compared to FSIs and their average firing frequency was lower in non-REM sleep. Rhythmic activity was observed in 21 out of 26 RSIs during spindle episodes with firing locked to different phases of spindle cycles: 12 cells increased firing near the trough, two cells near the peak, four cells at the descending phase and three cells at the ascending phase, respectively. Each cell recorded in REM sleep (n=14) showed elevated firing during theta activity in comparison to non-REM episodes either without significant phase preference (n=8) or with sustained phase-locked activity near the peak (n=2) or the trough (n=4) of the ongoing theta oscillation. Interestingly, REM theta phase relatedness was preserved during awake theta activity in each cell (n=14). Similar and rhythmic firing behavior during spindle versus theta activity was in n=3 cells and phase unrelated firing during spindles and theta was observed in n=3 cells; the rest of regular spiking cells (n=20) was differentially recruited to spindle and theta oscillations.

In conclusion, RSIs heterogeneously contribute to network activity during non-REM and REM sleep, partly in cooperation with FSIs during the trough of spindle oscillations. However, RSIs have additional contribution to network rhythms during theta periods when FSIs do not appear to be phase-locked in natural sleep.

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P106

IN VIVO LOCALIZATION OF DEEP BRAIN ELECTRODES IN MICE

Bálint Király[1,2,3], Diána Balázsfi[1], Ildikó Horváth[2], Nicola Solari[1], Domokos Máthé[2,4], Krisztián Szigeti[2], Balázs Hangya[1],*

1Lendület Laboratory of Systems Neuroscience, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary;
2Department of Biophysics and Radiation Biology, Semmelweis University, Budapest, Hungary;
3Department of Biological Physics, Eötvös Loránd University, Budapest, Hungary;
4CROmed Translational Research Centers, Budapest, Hungary

kiraly.balint@koki.mta.hu

Electrophysiology provides a direct readout of neuronal activity at a temporal precision only limited by the sampling rate. As neuroscience advances, rodent electrophysiology experiments are becoming harder, often involving recording from multiple small target areas during laborious behavioral training spanning up to 3-4 months. However, implanting deep brain structures, occasionally at unusual angles to avoid large blood vessels, still poses a significant challenge even for expert operators. Errors are only discovered at the end of the experiments by histological reconstruction.

To alleviate this, we developed a new method inspired by techniques used in human deep brain surgeries, which allows localizing electrodes in mice using in vivo structural imaging. We combined the high resolution information about bone landmarks by micro-CT scanning with the good soft tissue contrast of the MRI, which allowed to precisely localize implanted electrodes in a co-registered atlas coordinate system.

Our method enables arbitrating the success of implantation directly after surgery using in vivo, non-invasive techniques. Electrode coordinates could be determined with an accuracy within 150 µm, which is comparable to the precision of the gold standard histological reconstruction.

This accuracy allows precise adjustment of the recording depth with electrode microdrives or facilitates early termination in case of mistargeting. We estimate that this can save from 400 up to 1200 working hours per electrophysiology projects depending on the nature of the experiment. Furthermore, fast feedback on the potential causes of mistakes visualized in three dimensions could be of great help to surgeons in identifying and avoiding systematical errors.

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P107

SYNCHRONIZATION OF MEDIAL SEPTAL PACEMAKER NEURONS DURING HIPPOCAMPAL THETA GENERATION

Barnabás Kocsis[1], Richárd Fiáth[2], Andor Domonkos[3], Péter Barthó[2], Tamás Freund[3], Szabolcs Káli[3], István Ulbert[2], Viktor Varga[3], Balázs Hangya[1]

1Lendület Laboratory of Systems Neuroscience, Department of Cellular and Network Neurobiology- Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary;
2Institute of Cognitive Neuroscience and Psychology, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Budapest, Hungary;
3Cerebral Cortex Research Group, Department of Cellular and Network Neurobiology- Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary

kocsis.barnabas@tdk.koki.mta.hu

The medial septal region of the basal forebrain has been identified as responsible for hippocampal theta generation. According to the leading theory, rhythmically active individual 'pacemaker' cells, firing at their own frequencies, are synchronized to a common frequency and thus give rise to the hippocampal theta. However, experiments in which multiple septal neurons were recorded concurrently are rare and therefore the mechanisms of septal theta synchronization are still debated.

To address this, we aimed to decipher the network mechanisms of rhythm genesis in the medial septal circuit by analyzing multiple simultaneously recorded medial septal neurons from an anesthetized rodent model of hippocampal theta oscillation including both rats and mice (sensory stimulation evoked theta). Anaesthetized mouse recordings were performed with state-of-the-art high density silicon probes. Additional recordings were performed in awake drug-free mice (spontaneously forming theta).

Four medial septal rhythmicity groups were identified and their connections were explored. Network leader, constantly theta rhythmic neurons were tested to reveal their synchronization properties during theta. We have found that the biggest changes occured in their firing rate and weak indication pointed to burst parameter changes, frequency or phase synchronization.

To better understand the mechanisms underlying theta generation we also built a minimal network model consisting of theta rhythmic pacemaker units. We have demonstrated that this simple model can capture various features of septal theta genesis.

Aforementioned evidences suggested that instead of strong network connections, individual cell properties influences more the pacemaker synchronization and theta emergence.

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P108

IN VIVO GLUTAMATERGIC AND CHOLINERGIC INTERPLAY IN THE RAT HIPPOCAMPAL CA1 AREA: INTERACTIONS OF ALPHA7 NICOTINIC ACETHYLCHOLINE RECEPTOR EXCITATION WITH SPONTANEOUS AND NMDA-EVOKED FIRING ACTIVITY

Nagy LV, Bali ZK, Hernádi I

Translational Neuroscience Research Group, Centre for Neuroscience, Szentagothai Research Center, Department of Experimental Neurobiology, Faculty of Sciences, and Medical School, University of Pecs, Hungary

nagy.lili.veronika@gmail.com

Aims: Novel strategies for the treatment of neurocognitive disorders (NCDs) target the cholinergic system by the activation of α7 nicotinic acetylcholine receptors (nAChR) with selective agonists or with positive allosteric modulator (PAM) compounds. We aimed to investigate the local effects of an α7 nAChR agonist (PHA-543613) and two PAM compounds (PNU-120596, NS-1738) on the activity of CA1 hippocampal neurons, in vivo.

Methods: Extracellular firing activity of neurons was recorded in hippocampal CA1 region of anesthetized rats. NMDA, PHA-543613, PNU-120596, NS-1738 and MLA were locally administered in discrete time intervals using microiontophoresis.

Results: Results showed that the alpha7 nAChR agonist and PAMs have differential effects on the sensitivity of CA1 neurons to NMDA-evoked and spontaneous firing activity of the neurons. We found that PAMs predominantly and significantly increased both spontaneous and NMDA-evoked firing rate of the neurons, while after the application of PHA-543613 almost half of the neurons showed decrease of NMDA-evoked and spontaneous application. In most cases, NMDA-evoked firing responses to simultaneous application of PHA-543163 and PAMs showed a higher firing rate increase compared to mono-treatments, even if the agonist evoked an inhibitory effect on NMDA-evoked excitation. Hence, PAMs were able to reverse the inhibitory effect of the direct receptor agonist.

Conclusions: Most likely, the differential effects of agonists and PAMs might originate from the desensitization effect of the α7 nAChR agonist. The simultaneous activation of α7 nAChRs with PAMs may offer a better opportunity to enhance cognitive function compared to cholinergic agonists alone.

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P109

RECORDINGS OF SINGLE NEURON ACTIVITIES IN THE AMYGDALA OF BEHAVING, HEAD-FIXED MICE

Gergő A. Nagy, Bence Barabás and Norbert Hájos

'Momentum' Laboratory of Network Neurophysiology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest

nagy.attila.gergo@koki.mta.hu

Understanding the functional organization of amygdala neural circuits requires stable electrophysiological recordings of single neuronal activities in awake mice performing complex behavioural tasks.

Head-fixed, in vivo experimental configurations provide substantial recording stability. However, due to technical constraints, experiments in head-fixed conditions typically limited to behavioural tasks guided by sound or distal visual cues in virtual environments which provide little tactile information for the animals. The absence of tactile stimuli affects neural activity patterns, increase the anxiety levels and hinders the learning ability of the mice.

To address these drawbacks, we aimed to develop an approach to perform stable juxtacellular and extracellular recordings of single neuron activities from the amygdala of awake, head-fixed mice while studying its behaviour in Neurotar's Mobile HomeCage. This recently developed platform allows the mice to navigate in an air-floating maze during the experiments.

Our results indicate that the presence of tactile stimuli allow training of mice in fear- and reward-related behavioural tasks with high efficiency. Recordings of local field potentials indicate that hippocampal oscillatory activity patterns are similar to those observed in freely moving mice. Furthermore, using either juxtacellularly positioned glass electrodes or silicon probes we were able to record stable, well-isolated single neuron activities from the amygdala.

In summary, we successfully utilized an approach that, while providing increased behavioural freedom, allow us to perform stable juxtacellular and extracellular recordings of single unit activities from the amygdala of head-restrained, awake mice.

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P110

THE BASAL FOREBRAIN MAY PROVIDE A LINK BETWEEN LOCOMOTION AND LEARNING

Katalin Sviatkó[1,2], András Széll[3], Panna Hegedüs[1,2], Anita Bánhidi[1],[4], Balázs Hangya[1]

1Lendület Laboratory of Systems Neuroscience,Department of Cellular and Network Neurobiology, Institute of Experimental Medicine – Hungarian Academy of Sciences, Budapest,H-1083, Hungary;
2János Szentágothai Doctoral School of Neurosciences, Semmelweis University, Budapest, H-1085, Hungary;
3Department of Measurement and Information Systems, Budapest University of Technology and Economics, Budapest, H-1117, Hungary;
4Eötvös Lorand University, Faculty of Science Institute of Biology, Budapest,H-1117, Hungary

sviatko.katalin@koki.mta.hu

Cortical processing depends on brain states that influence animal behavior. Brain states are controlled by the coordinated activity of multiple subcortical neuromodulatory centers. Among these the basal forebrain has widespread projections thought to mediate multiple cognitive functions. From these, the GABAergic projection has been implicated in controlling the locomotion-related theta oscillation and the glutamatergic projection can directly control animal speed. On the other hand, cholinergic cells respond rapidly and reliably to reinforcement that is likely important for learning. Therefore we hypothesize a relationship between basal forebrain neuronal activity, locomotion and learning.

To directly test this, head-fixed mice were placed on a wheel and trained on an auditory Pavlovian cued outcome task in which two pure tones predicted likely reward or likely punishment. We quantified how well mice learned the task by measuring anticipatory licking. This experimental design allowed mice to run or stay still voluntarily during the task. We monitored neuronal activity in the medial septum using tetrode electrodes. Therefore it was possible to examine whether there were correlated changes in basal forebrain neuronal activity, behavioural performance and learning across 'standing still' and running states.

We found that mice trained on wheel learned faster. When allowed to run freely, mice tended to run after reinforcement delivery, which could reflect approach or escape responses. Neurons displayed a diversity of responses to behaviourally relevant events with dominant subpopulations showing activation or suppression after air puff delivery. These medial septal cell types may convey locomotion dependent learning signals via the septo-hippocampal pathway.

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FUNCTIONAL CONNECTIVITY BETWEEN THE LATERAL HYPOTHALAMUS AND TWO MAIN CORTICAL AREAS, ANTERIOR CINGULATE AND ORBITOFRONTAL CORTEX, INVOLVED IN DECISION-MAKING

Sara Karimi[1], Mohammad Ismail Zibaii[2], Gholamali Hamidi[1], Abbas Haghparast[3]

1Physiology Research Center, Kashan University of Medical Sciences, Kashan, Iran;
2Laser and Plasma Research institute, Shahid Beheshti University, Tehran, Iran;
3Neuroscience Research Center, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

sarakarimi59@gmail.com

Anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) are two main parts of medial prefrontal cortex (mPFC), which have important roles in cognitive behaviors like decision-making. The Lateral hypothalamus (LH) is another important region in the brain, which has a well position in the cerebral hemisphere, with a considerable connectional network. Behavioral and electrophysiological studies have suggested the significance of the functional connections between the mPFC and the LH.

In the present study, the effect of reversible inactivation of the LH on firing rate and activity pattern of the ACC or OFC neurons was investigated by using in vivo single-unit recording technique in the rats. After 10 min of baseline recording from the ACC/ OFC region, lidocaine 4% or vehicles (saline or DMSO 12%) was microinjected into the LH by using a Hamilton microsyringe, and the spontaneous firing activity continued to be recorded for 40-min period.

Results showed that reversible inactivation of the LH excited 5 out of 12 neurons and inhibited 6 neurons in the ACC. Also it could excite 8 and inhibit 6 neurons out of 14 neurons in the OFC.

It seems that activation of the LH's projections especially orexinergic projections have a crucial role in management of neural activity of ACC and OFC.

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HOW ATTENTION SHAPES SONG PERCEPTION IN JUVENILE ZEBRA FINCHES DURING SONG LEARNING

Jelena Katic and Yoko Yazaki-Sugiyama

Okinawa Institute of Science and Technology Graduate University, Japan

jelena.katic@oist.jp

Juvenile zebra finches learn to sing via vocal communications with their fathers (tutors). Song learning improves through social interactions with tutors, compared to passive listening to recorded tutor songs. This suggests that high attention level, induced by social interactions, enhances song learning.

We investigated how attention regulates zebra finch song learning by recording neuronal activities in the attention control area, nucleus locus coeruleus (LC), and the higher auditory area, caudomedial nidopallium (NCM), where tutor song memories are suggested to be stored (Yanagihara & Yazaki-Sugiyama, 2016). We chronically recorded extracellular single-unit activity from LC and NCM neurons of freely behaving juvenile zebra finches for three days before, and three days during tutoring. Neurons were tested for auditory responsiveness to playbacks of various recorded songs, and live tutor songs.

LC neurons showed unbiased responses to various song playbacks, while responded greater to live tutor songs. LC neurons, with high spontaneous tonic firing, exhibited offset responses to live tutor songs by decreasing firing rates. Anatomical analysis showed that LC neurons, which were activated during tutoring, project to the NCM. Proportions of NCM neurons with unbiased responses decreased with tutoring, whereas the proportions of NCM neurons with selective responses to the tutor song increased. As LC neurons, tutor-selective NCM neurons showed an offset response to live tutor singing by decreasing their firing rates.

We suggest that social interactions with tutors modulate neuronal activity of the LC, which affects auditory responses of the NCM, resulting in tutor song selective perception and memory formation.

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P113

PRESYNAPTIC ACTIVATION OF 5-HT1B RECEPTORS INHIBITS PROPRIOCEPTIVE SENSORY INPUTS TO JAW-CLOSING MOTONEURONS

Tomio Inoue[1], Ai Nagata[1,2], Kiyomi Nakayama[1], Masanori Dantsuji[1], Shiro Nakamura[1], Ayako Mochizuki[1], Koutaro Maki[2]

1Department of Oral Physiology, Showa University School of Dentistry, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan; 2Department of Orthodontics, Showa University School of Dentistry, 2-1-1 Kitasenzoku, Ota-ku, Tokyo 145-8515, Japan

inouet@dent.showa-u.ac.jp

Aims: Sensory information from periodontal receptors and jaw-muscle spindles is transmitted by primary afferent neurons in the mesencephalic trigeminal nucleus (MesV) to jaw-closing motoneurons (JCMNs), contributing to reflex modulation of jaw-muscle force during mastication. Dense 5-HT terminals are found in both the MesV and trigeminal motor nucleus. However, the mechanism of modulation by 5-HT of synaptic transmission from MesV afferents to the JCMNs has not been characterized. Using whole-cell recordings of brainstem slice preparations obtained from postnatal 8- to 12-day-old juvenile Wistar rats, we examined the effects of 5-HT on excitatory postsynaptic potentials (eEPSPs) in JCMNs evoked by MesV afferent stimulation.

Methods: Transverse brainstem slices at a thickness of 500 micrometers and containing the MesV and trigeminal motor nucleus were cut using a vibrating microtome. To evoke eEPSPs in JCMNs, stainless steel concentric bipolar stimulating electrodes were placed on the trigeminal motor nerve in each slice.

Results: Bath application of 10 micromolar 5-HT decreased the peak amplitude of eEPSPs in JCMNs. That inhibition was mimicked by the 5-HT1B receptor agonist CP-93129, but not the 5-HT1A receptor agonist 8-OH-DPAT, while inhibition was antagonized by the 5-HT1B receptor antagonist SB-224289, but not the 5-HT1A receptor antagonist WAY-100635. Furthermore, CP-93129 increased the paired-pulse ratio of eEPSPs and also decreased the frequency, but not the amplitude, of miniature excitatory postsynaptic currents.

Conclusion: Activation of presynaptic 5-HT1B receptors inhibits excitatory synaptic transmission from MesV afferents to JCMNs. Such inhibition may contribute to decrease sensory feedback during mastication.

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P114

DUAL ACTION OF D1 AND D2 DOPAMINE RECEPTORS ACTIVATION IN NUCLEUS INCERTUS

Agata Szlaga, Anna Gugula, Anna Blasiak

Department of Neurophysiology and Chronobiology, Institute of Zoology and Biomedical Research, Jagiellonian University in Krakow, Poland

agata.szlaga@doctoral.uj.edu.pl

Aims: Nucleus incertus (NI) is a main source of relaxin-3 in the brain and is involved in control of stress, food intake and arousal related processes. Relaxin-3 is an orexigenic (food intake promoting) peptide with stronger actions in female than male rats. The goal of the current study was to assess the involvement of dopaminergic receptors in modulation of NI neurons activity.

Methods: The influence of D1 and D2 receptor agonists on NI neurons activity was tested using whole-cell patch clamp technique. Combined tract-tracing with anti-tyrosine hydroxylase (TH) immunohistochemical staining was used to indicate the source of TH in the NI.

Results: Electrophysiological recordings revealed expression of functional D1 and D2 receptors on NI neurons. Bath application of D1R agonist SKF-38393 and D2R agonist quinpirole exerted both inhibitory and excitatory response of recorded cells (increase in outward and inward current, respectively). Surprisingly, in standard ACSF in majority of recorded neurons excitatory action of D2R agonist was observed. Both excitatory and inhibitory actions of quinpirole persisted in the presence of tetrodotoxin and GABA/glutamate receptors antagonists, what indicates postsynaptic site of its action. Tract-tracing technique allowed us to indicated hypothalamic dopaminergic groups A11 and A13 as a source of TH-immunoreactive fibers in the NI.

Conclusions: TH-immunoreactive fibers arising from A11 and A13 are possible source of dopamine in the NI. Taking into account that both A11 and A13 are sensitive to sex hormones, their projections to NI may underlie sex differences in relaxin-3 orexigenic effect.

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P115

SUPERIOR COLLICULI CONTROL FIRING OF THE CONTRALATERAL ROSTROMEDIAL TEGMENTAL NUCLEUS – AN OPTOGENETIC STUDIES IN THE RAT

Kamil Pradel, Tomasz Błasiak

Department of Neurophysiology and Chronobiology, Institute of Zoology and Biomedical Research, Jagiellonian University, Cracow, Poland

kamil.pradel@doctoral.uj.edu.pl

Dopaminergic (DA) neurons of the midbrain are, among others, responsible for controlling animal's orienting and movement towards salient and/or rewarding stimuli. DA neuron firing is regulated by many brain structures, however the sensory input is provided predominantly by the ipsilateral superior colliculus (SC). Tract tracing experiments suggest that SC also innervates the contralateral rostromedial tegmental nucleus (RMTg) – the main inhibitory input to dopaminergic neurons. The aim of this study is to describe physiology and anatomy of the SC-RMTg circuit.

Electrophysiological experiments combined with optogenetics were performed to investigate this circuit. Sprague-Dawley rats were injected stereotaxically into the SC with adenoviral vectors containing Channelrhodopsin-2 (ChR2) and yellow fluorescent protein (eYFP) genes. After ChR2 (blue light-sensitive cation channel) expression, in vivo electrophysiological recordings were conducted. RMTg neurons located contralaterally to the SC injection were recorded using 32-channel silicon probes, while the SC was optogenetically stimulated with laser blue light (473 nm). After each experiment expression of eYFP as well as location of the recorded neurons within the RMTg were histologically verified.

Obtained results revealed that firing of many of the RMTg neurons is increased by optogenetic stimulation of the contralateral SC. Additionally, eYFP-positive, SC-originating axon terminals within the borders of the contralateral RMTg were observed. Such brain wiring might have important implications for the lateralisation of motivation-oriented behaviours.

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P116

BRAIN STATE DEPENDENT RESPONSES OF DOPAMINERGIC NEURONS TO THE AVERSIVE STIMULUS

Izowit G.[1], Walczak M.[1], Drwięga, G.[2], Pradel, K.[1], Solecki, W.[2], Błasiak T.[1]

1Department of Neurophysiology and Chronobiology, Institute of Zoology and Biomedical Research, Jagiellonian University, Cracow, Poland;
2Department of Neurobiology and Neuropsychology, Institute of Applied Psychology, Jagiellonian University, Cracow, Poland

gabriela.izowit@student.uj.edu.pl

For a long time it was thought that midbrain dopaminergic neurons respond uniformly to aversive or noxious stimuli, showing short latency, transient pause in firing. However, recent studies have revealed a subpopulation of VTA dopaminergic neurons that exhibit excitatory responses to the footshock (aversive stimulus). Furthermore, independent studies have shown that both the level and pattern of VTA and SNc dopaminergic neurons' activity are modulated by ongoing brain states under urethane anaesthesia.

We hypothesized that the responses of VTA/SNc dopaminergic neurons to noxious stimuli are also modulated by alternating states of the brain.

We carried out in vivo recordings of dopaminergic neurons' responses to the electrical footshock, in urethane anaesthetized rats. In one set of experiments we used single unit juxtacellular recording-labelling technique. In parallel set of experiments, in order to optogenetically identify recorded dopaminergic neurons, we used transgenic rats (Sprague-Dowley TH-Cre+/-) transduced with adeno-associated virus inducing channelrhodopsin-2 along with EYFP genes expression in a Cre-dependent manner. We observed two previously described subpopulations of VTA and SNc dopaminergic neurons – either excited or inhibited by aversive stimulus. Interestingly, our observations led us to discover the third, previously unknown, population of dopaminergic neurons, which is characterized by dynamic, brain state dependent changes in the type of response to the aversive stimulus. These neurons are inhibited during REM-like brain state, but change the type of response to excitation during NREM-like brain state.

This study verifies and supplements our current knowledge about the reaction of midbrain dopaminergic neurons to the aversive stimuli.

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POTASSIUM CHANNELS ARE IMPORTANT FOR THE MOBILITY OF BV2 MICROGLIA

Ruxandra-Elena Anton[1], Violeta Ristoiu[1], Alexandru-Florian Deftu[1,2]

1Department of Anatomy, Animal Physiology and Biophysics, Faculty of Biology, University of Bucharest, Romania;
2The Research Institute of the University of Bucharest (ICUB)

antonruxandraelena@yahoo.com

Aims: The selective inhibition of potassium channels can produce different changes in the activity of the cells and can thus offer important information about their role. Many functions of microglial cells are dependent on ion channels but there is no clear study showing the contribution of Kir channels in cellular migration. In this study we investigated how UK-78282 a specific inhibitor for Kir2.1 potassium ion channels might interfere with microglial migration.

Methods: The BV2 microglial cells were seeded at 2x104 in DMEM supplemented with 10% FBS and 1% P/S, and were incubated for 3 h or 6 h at 37°C and 5 % CO2. The migration was tested using inserts with 8 µm pores. Subsequently, the cells were fixed with 4% PFA, the nuclei were stained with Hoechst (# 33342) and the images on the diagonal of the insert were captured with a 10x objective using an Olympus epifluorescence microscope.

Results: Our experiments showed that following the incubation of microglial cells for 3 h with 10 µM UK-78282 the migration rate (273.9 ± 39.36, N = 22) decreased significantly in comparison to the control condition (403.8 ± 44.96, N = 22, $P < 0.05$). On the other hand, incubation of BV2 cells for 6 h with 10 µM UK-78282 did not result in a reduction in the migration rate (251.1 ± 57.56, N = 15) compared to the control condition (302.9 ± 50.58, N = 20, $P > 0.05$).

Conclusion: The inhibition of Kir2.1 potassium ion channels altered the microglial mobility after short term incubation and further experiments are needed to indicate the contribution of these ionic channels in cellular migration in vivo.

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P118

ELECTROCORTICOGRAPHICAL RECORDINGS IN A ROBUST IN VIVO MODEL OF EPILEPTIC SEIZURES IN MICE

Marina Cozma[1] ,Miruna Costreie[1], Miruna Rascu[1], Mihai Stancu[1], Alexandru Calin[2], Andrei Ilie[2], John Jefferys[2], Ana-Maria Zagrean[1], Colin Akerman[2]

1Physiology and Neuroscience, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania;
2Department of Pharmacology, University of Oxford, Oxford, UK

marina.cozma@stud.umfcd.ro

Aims: Electroencephalography is used in clinical settings for investigating neurological disorders, such as epilepsy. A more precise variant of this method, electrocorticography (ECoG), is frequently used in animal experiments. The objective of this study was to build an ECoG setup that would allow recordings from freely-moving animals during delivery of the convulsant agent, 4-aminopyridine (4-AP) and to examine correlations between brainwave characteristics and behavior during epileptic seizures.

Methods: We used four C57BL/6 mice, which were accommodated to a 12 hour day-night cycle, with food and water available ad libitum. The electrodes (A, B, C) were placed just posterior to the bregma and on the hemisphere where the cannula was mounted (A), in the same opening as the cannula (B), and on the contralateral side of the cannula, at the equivalent coordinates (C). Electrode A was used as a reference. The cannula was placed as the final step. The electrodes were connected to a wireless transmitter that was attached to a fluid swivel. The swivel allowed free movement and 4-AP infusion at the same time, which was essential for unimpaired observations of seizures and epileptic behavior.

Results: The resulting setup provided accurate portions of synchronized ECoG and video streams, which were then compared. Preliminary analysis revealed that moderate epileptic behavior was not always accompanied by ECoG manifestations, while peri-seizure behaviors had a strong ECoG component.

Conclusions: This is a powerful tool to assess different convulsant agents, the efficacy of anti-epileptic drugs, or underlying cellular mechanisms, like the action of inhibitory interneurons in the hippocampus.

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P119

ALTERED PERIPHERAL NERVE TRPV4 FUNCTION IN A MOUSE MODEL OF DEMYELINATING CHARCOT-MARIE-TOOTH DISEASE

Loredana Cumpana[1,2], Tudor Selescu[1], Alexandru Babes[1], Christian Krarup[2,3], Mihai Moldovan[2,3]

1Department of Anatomy, Physiology, and Biophysics, University of Bucharest, Faculty of Biology, Bucharest, Romania;
2Department of Neuroscience, University of Copenhagen, Copenhagen, Denmark;
3Department of Clinical Neurophysiology, Rigshospitalet, Copenhagen, Denmark

loredana.cumpana42@gmail.com

Demyelinating Charcot-Marie-Tooth neuropathy type 1A (CMT1A) resulting from peripheral myelin protein 22 KDa (PMP22) overexpression is the most common hereditary motor and sensory neuropathy in humans. The mechano-osmosensor Transient Receptor Potential Vanilloid 4 (TRPV4) polymodal ion channel is expressed in several types of glial cells. This study aimed to investigate TRPV4 function in peripheral nerves of a well-established CMT1A model, the PMP22 transgenic mice (PMP22tg).

Investigations were carried out in mature PMP22tg and wild type (WT) littermates by in vivo neurophysiological studies under anesthesia and temperature control. The tibial nerve was stimulated at the ankle, and the evoked compound muscle action potential was recorded from the plantar muscles. Changes in multiple measures of axonal excitability by threshold-tracking were investigated after an intermittent burst stimulation protocol with 250 ms trains of 100 Hz, repeated every other second for 1 hour. Primary Schwann cell cultures obtained from the sciatic nerves were used for calcium imaging experiments.

Following burst stimulation, PMP22tg showed a marked increase in the resting I/V conductance which did not occur in the presence of the selective TRPV4 agonist GSK1016790A (0.04 mg/kg). TRPV4 activation had a smaller effect on WT excitability changes. Consistently, calcium imaging in Schwann cell cultures found a lower half maximal effective concentration for TRPV4 activation in PMP22tg than in WT. Taken together, these data suggest that PMP22tg Schwann cells have an increased susceptibility for TRPV4 activation which alters the axonal excitability homeostasis during prolonged repetitive activity.

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P120

FUNCTIONAL ABNORMALITIES IN THE CEREBELLO-THALAMIC-CORTICO NETWORK IN AN GNAL (+/-) ANIMAL MODEL OF DYSTONIA

Elena Laura Georgescu[1,2], *, Fabien Menardy[1],*, Hind Baba Aïssa[1], Assunta Pelosi[3], Leonardo Belluscio[4], Denis Hervé[3], Clément Léna[1], Daniela Popa[1,2]

1Institut de Biologie de l'Ecole Normale Supérieure, INSERM U1024, CNRS UMR8197, Paris, France;
2Division of Physiology and Neuroscience, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania;
3Institut du Fer à Moulin, INSERM UMR-S 839, Paris, France;
4National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA

* These authors contributed equally

laura.georgescu@umfcd.ro

Aims: Strong evidence indicates that dystonia, an extremely disabling motor disease, is associated with functional alterations in cerebello-cortical connections. Yet, how cerebellum drives these abnormal motor circuit and how it participates to dystonic attacks remains poorly understood.

Methods: In order to study the functional state and role of the cerebello-cortical pathway in dystonia, we use heterozygous animals carrying GNAL gene (GNAL+/-). A role of the mutation in GNAL gene coding for an olfactory type G-protein alpha subunit (GalphaOlf) has been recently shown in primary dystonia in humans. Moreover, GalphaOlf is highly expressed in the striatum and in the cerebellum. The mutation in mice causes perinatal death in its homozygous form, but limited motor dysfunction (hyperlocomotion) in its heterozygous form; heterozygous mutants are thus close to non-manifesting gene carriers in humans and can be used as models for dystonia.

Results: In the present study, we investigate the behavior and neurophysiological impact of cerebellar optogenetic stimulations on the motor circuit activity during normal movement and during dystonic attacks that were triggered pharmacologically in the GNAL+/- animal model of dystonia. We observe changes in the functional connectivity in the cerebello-cortical pathway during the expression of the motor syndrome in GNAL+/- mice such as a decreased firing rate in the intralaminar thalamus in GNAL+/- mice compared with controls. Also, we obtained preliminary evidence for beneficial effect of the cerebellar stimulation on motor activity in GNAL+/- mice.

Conclusion: Our results provide new insights on the pathophysiological processes taking place in the cerebello-cortical networks in dystonia.

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P121

IBA-1 SILENCING ALTERS MOBILITY OF BV2 MICROGLIA

Andreea-Violeta Grosu, Gisela Gaina, Alexandru-Florian Deftu, Roxana-Olimpia Gheorghe, Violeta Ristoiu

Department of Anatomy, Animal Physiology and Biophysics, Faculty of Biology, University of Bucharest, Bucharest, Romania

grosu.andreea96@gmail.com

Aims: Ionized calcium binding adaptor molecule 1 (Iba-1) is a microglia/macrophage specific marker, a cytoskeletal protein which forms complexes with F-actin, modulating cellular architecture. Our aim for this study was to test the effect of Iba-1 silencing on BV2 microglia migration and on macrophages mobility in neuropathic conditions (SNL model).

Methods: In vitro, BV2 cells were transfected with Iba-1 small interfering RNA (siRNA) and scrambled siRNA (scRNA), as a negative control. The impact on migration was assessed by transmigration, chemotaxis, chemokinesis and invasion assays, which involved quantifying the number of cells that migrated through 8µm pores. In vivo, Iba-1 siRNA or scRNA/PBS was injected into the L5 DRG of injured/uninjured male Sprague-Dawley rats. L5 DRGs were collected 5 days after surgery and spatial interaction between macrophages and neurons was analysed immunohistochemically, using antibodies to Iba-1 (for macrophages) and to NF200(for neurons).

Results: Our study revealed that following the silencing of Iba-1 protein, BV2 microglia presented a lower migration rate as quantified by four assays: transmigration, chemotaxis, chemokinesis and invasion. After SNL, the Iba1(+) macrophages from DRG become activated and migrate towards neurons, clustering mostly around NF200(+) large neurons. Silencing Iba-1 did not reduce the macrophages ability to form perineuronal rings, which nevertheless looked looser than without treatment.

Conclusions: Iba-1 silencing significantly affects microglial/macrophage migration rate, which could have an important effect in treating some diseases or conditions associated with an excessive microglial/macrophage activation, such as glioblastomas and neuropathic pain.

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P122

EARLY DETECTION AND MONITORING OF CEREBRAL ISCHEMIA USING A CALCIUM RESPONSIVE MRI PROBE

Goran Angelovski, Tanja Savić, Giuseppe Gambino, Vahid Bokharaie, Hamid R. Noori and Nikos K. Logothetis

Max Planck Institute for Biological Cybernetics, Tuebingen, Germany

goran.angelovski@tuebingen.mpg.de

Aims: The extent of brain injury caused by cerebral ischemia depends primarily on its duration, thus its monitoring is of crucial importance. Considering that extracellular Ca^{2+} decreases dramatically during ischemia[1,2], an imaging method that tracks *in vivo* variations of $[Ca^{2+}]_e$ thus enabling monitoring of the intensity and duration of cerebral ischemia would be of paramount importance. Here we report development of an fMRI method to monitor the progress of ischemia by means of Ca-responsive MRI probe.

Methods: Two probes, responsive Gd_2L or non-responsive Gd_2L as a control were intracranially infused in Wistar rats, while cerebral ischemia was caused using remote transient middle cerebral artery occlusion (tMCAo). fMRI consisted of a series of T_1w MRI acquisitions, while controls included infusion of probes, without tMCAo. Data analysis was based on K-means clustering and the signal de-trending.

Results: Clustering displayed the co-centric pattern of the T1w signal. De-trended clustered signals showed up to 5% signal change for tMCAo experiments with Gd2L1, while those with Gd2L2 and control experiments showed no signal alterations.

Conclusions: We report successful fMRI approach for monitoring of the cerebral ischemia using bio-responsive MRI probe. This method detects the ischemic onset promptly, also revealing immediate changes during reperfusion that is crucial for the choice of therapy and subsequent recovery. Moreover, this molecular fMRI technique could allow the visualization and mapping of neural signaling directly, using calcium as its direct indicator, supplementing the use of conventional fMRI based on BOLD signal.

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P123

KV1.3 AND KV1.5 CHANNELS ARE INVOLVED IN BV2 CELLS' MIGRATION

Mihail Ghenghea[1], Angelica Tuchiluș[1], Violeta Ristoiu[1], Alexandru Deftu[1,2]

1Department of Anatomy, Animal Physiology and Biophysics, Faculty of Biology, University of Bucharest, Romania ;
2The research Institute of the University of Bucharest (ICUB), Bucharest, Romania

m.ghenghea@yahoo.com

Aims: Microglia are the resident immune cells in the central nervous system, strongly involved in response to injury and regulatory processes critical for development. The ion channels expressed on this cells membrane are associated with microglia activity. Kv1.3 and Kv1.5 are voltage-gated potassium channels involved in many cellular processes. In this study we highlighted the presence of these potassium channels through patch clamp measurements in BV2 microglial cells and showed their role in migration.

Methods: Patch-clamp recordings were made in the whole-cell configuration, on BV2 cells after 24 h in culture. UK-78282 for Kv1.3 and S9947 for Kv1.5 were used as specific inhibitors. The scratch assay test was used to quantify microglial migration in culture.

Results: Our patch clamp experiments showed that UK-78282 significantly inhibited the currents at a +40 mV step (from 157.247 pA in control condition to 51.913 pA after the treatment), while at -120 mV step the inhibitory effect was not so pronounced (from -189.911 pA in control conditions to -161.358 pA after the treatment). S9947 significantly inhibited the current at both +40 mV step (from 146.622 pA to 42.131 pA) and the -120 mV step (from -265.118 pA to -200.475 pA). Scratch assay experiments indicated the contribution of these potassium channels to BV2 migration.

Conclusion: Our experiments show that Kv1.3 and Kv1.5 may contribute to microglia migration. Further experiments are needed to investigate how voltage gated channels may induce cytoskeleton changes associated with migration.

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P124

IN VIVO CHEMOGENETIC MODULATION OF SEIZURE ACTIVITY IN MICE

Raluca-Elena Mitran[1], Patricia-Demetria Popovici[1], Miruna Rascu[1], Maria-Miruna Costreie[1], Vlad-Petru Morozan[1], Mihai Stancu[1], Alexandru Calin[2], Andrei Ilie[2], Ana-Maria Zagrean[1], John Jefferys[2], Colin Akerman[2]

1Physiology and Neuroscience, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania;
2Department of Pharmacology, University of Oxford, UK

ralucamitran972@gmail.com

Aims: Epilepsy is often characterised by an imbalance between excitation and inhibition of the neuronal networks in the brain. Parvalbumin-expressing (PV), somatostatin-expressing (SST) and vasoactive intestinal peptide-expressing (VIP) interneurons are thought to differentially regulate network activity by targeting distinct sub-cellular post-synaptic domains of excitatory neurons, or even other inhibitory interneurons. Our objective was to establish a reliable murine in vivo seizure model, and to use excitatory DREADDs (designer receptors exclusively activated by designer drugs) to investigate the capacity of PV, SST and VIP interneurons to modulate epileptic behaviour.

Methods: We used three strands of mice expressing Cre recombinase in either of the PV, SST or VIP interneuron populations. Adeno-associated virus delivering the double-floxed DREADDs construct was used to transduce hippocampi bilaterally. After viral expression was achieved, the mice received a cannula implant which was used for the gradual intra-hippocampal infusion of the convulsant agent, 4-aminopyridine. DREADDs were activated by intraperitoneal injections of clozapine-N-oxide prior to the infusion. EEG activity was scored using the Racine scale.

Results:When PV interneurons were recruited, the probability of reaching a generalised seizure decreased by 45%, whereas when SST or VIP interneurons were stimulated, no significant probability change was recorded. Epileptic behaviour was confirmed to be associated with seizure-specific EEG alterations.

Conclusions: Our study stands as a proof of concept, indicating that, depending on which interneuron subtype is recruited, specifically stimulating distinct interneuron populations of the hippocampus via excitatory DREADDs has the potential to significantly alleviate epileptic behaviour in freely behaving mice.

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TASK-RELATED EEG REACTIVITY FOLLOWING TRANSCRANIAL DIRECT CURRENT STIMULATION OF THE DORSOLATERAL PREFRONTAL CORTEX

Alexandru Paslaru[1], Dorottya Szocs[1], Stefan Teodorescu[1], Cosmin-Andrei Şerban[2,3],[4], Ana-Maria Zăgrean[6], Leon Zăgrean[6], Mihai Moldovan[1],[5]

1Division of Physiology and Neuroscience, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania;
2Physics Department, University of Bucharest, Romania;
3Termobit Prod SRL, Bucharest, Romania;
4FHC Inc, Bowdoin, ME, USA;
5Department of Neuroscience, Panum, University of Copenhagen, Copenhagen, Denmark

catalin.paslaru@umfcd.ro

The dorsolateral prefrontal cortex (DLPFC) comprises a widely connected network that mediates key executive functions necessary for the cognitive control of behavior. Application of a weak transcranial direct current stimulation (tDCS) over DLPFC was found to alter a wide range of active behaviours although little is known about the tDCS effects on passive tasks. The aim of this study was to investigate the task-related EEG changes by tDCS over DLPFC in a group of healthy student volunteers.

Simultaneous tDCS and EEG recordings were carried out using a simplified 8-channel montage. Anodal tDCS (excitatory) with 1.5 mA was delivered via large sponge electrodes over the left DLPFC (F3) against FP2 as reference. For the active task we asked the participants to play an engaging 1-minute virtual reality game in which they had to solve a custom-developed maze. For the passive task the subjects were required to listen to 1-minute epochs alternating salient subjects own name (SON) stimuli with name played in reverse(rSON) as generated by a native language voice synthesizer. A whole-brain reactivity index was defined to quantify the amount of spectral EEG changes during the task as compared to resting EEG prior to the task. We found that the largest increase in reactivity after tDCS was in the passive SON task.

Our data suggest that in conscious brains, DLPFC tDCS can increase the EEG reactivity to salient auditory stimuli. This opens the possibility to use the tDCS modulation of EEG reactivity as a tool to assess altered states of consciousness.

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EFFECTS OF TRANS-RESVERATROL AND CITICOLINE SUPPLEMENTED MATERNAL DIET ON THE BEHAVIOR OF OFFSPRING RATS SUBJECTED TO PERINATAL ASPHYXIA

Artsiom Klimko, Sebastian Isac, Vlad Zeca, Anca Maria Panaitescu, Leon Zagrean, Ana-Maria Zagrean

Physiology and Neuroscience Division, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

klimkoartiom@gmail.com

We previously showed that maternal diet impacts on post-asphyxia hippocampal injury in rats. This study investigates the early and late behavioral effects of trans-resveratrol (tRESV) and citicoline maternal dietary supplementation in offspring subjected to perinatal asphyxia (PA).

Female Wistar rats received from weaning and until their pups reached postnatal day 7 (PND7), either standard diet or a supplemented diet, with tRESV (50mg/kg body-weight/day) or citicoline (200mg/kg body-weight/day). PND6 male offspring were subjected to 90-minute PA (9% O2, 20% CO2) and grown to maturity. The loss of righting reflex (LRR) was assessed for 2h immediately post-asphyxia. The behavioral tests, open field-test (OFT), novel object recognition test (NORT), T-Maze and forced swimming test (FST), were assessed at maturity.

The tRESV vs standard diet group showed a decrease in LRR ($p=0.004$), while in the T-maze test it had a higher rate of alternating the maze's arms ($p=0.004$), without significant changes in OFT, NORT and FST. The citicoline vs standard-diet group, showed a lower total immobility time in FST ($p=0.02$), a higher rate of alternating the arms of the maze in T-maze test ($p=0.0002$), without differences for the other tests.

In conclusion, tRESV supplementation had an immediate beneficial effect by reducing asphyxia-induced convulsive activity, and a long-term effect by improving behavioral tests for locomotor capacity, desire for exploration and plastic memory. Citicoline produced minor improvements in behavioral tests, with no early beneficial effect. Further studies are needed to understand the early and long-term impact of maternal diet on offspring brain vulnerability to perinatal asphyxia.

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CEREBELLAR CONTRIBUTION TO OSCILLATORY CORTICAL ACTIVITY IN DYSTONIA

Steopoaie Alexandru[1], Georgescu Elena Laura[1,2], Georgescu Ioana Antoaneta[1], Zahiu Denise[1], Tirlea Alexandru[1], Pana Adrian[1], Nichita Adriana Monica[1], Zagrean Ana-Maria[1], Popa Daniela[1,2]

1Division of Physiology and Neuroscience, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania;
2Institut de Biologie de l'Ecole Normale Supérieure, INSERM U1024, CNRS UMR8197, Paris, France.

razvan.steopoaie@stud.umfcd.ro

The cerebello-cortical network modulates the neural activity synchronization, especially in the sensorymotor cortices, which are responsible for motor control and learning. Abnormal signalling in the cerebello-thalamo-cortical pathways can alter the brain oscillatory activity and cause movement disorders.

This study's aim was to find the cerebellar contribution to oscillatory brain activity, particularly in the case of dystonia.

We evaluated the oscillatory cortical activity and connectivity of the motor, somatosensory and parietal cortices by applying kainic acid on top of the cerebellar vermis in mice. This kainic acid induced dystonia model helped us investigate the electrocorticogram (ECoG) power spectral density and coherence between these cortices before and during dystonic attacks.

We showed that repeated applications of kainic acid into the cerebellar vermis, for five consecutive days, generate reproducible dystonic motor behavior. We found a phenomenon of permanent adaptation with a change of baseline locomotor activity coupled to an ECoG gamma band increase in all cortices. Moreover, after kainate administration, we observed an increased muscular activity, but less signs of dystonia, together with modulations of the ECoG power-spectra with a gamma band increase in motor, parietal and somatosensory cortices. However, a reduced coherence was found between the motor cortex and somatosensory/parietal cortices in all measured frequency bands compared to baseline. The imaginary part of the coherence was also computed to estimate the coherence avoiding contamination by volume conduction.

In conclusion, cerebellar dysfunction reveals a disruption of the coordination of neuronal activity across the cortical somatosensory/parietal network, which may underlie deficits in motor skills.

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ASSESSMENT OF THE RAT EPILEPTIC BRAIN BY BURST-SUPPRESSION EEG REACTIVITY

Dorottya Szocs[1], Paslaru Alexandru Catalin[1], Stancu Mihai[1], Pavel Bogdan[1], Zahiu Carmen Denise[1], Zagrean Ana Maria[1], Zagrean Leon[1], Moldovan Mihai[1,2]

1Division of Physiology and Fundamental Neuroscience, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; 2Department of Neuroscience, University of Copenhagen, Copenhagen, Denmark

dorottya.szocs18@gmail.com

Absence seizures are characterized behaviorally by a paroxysmal loss of consciousness of abrupt and sudden onset and offset that is associated with bursts of bilaterally synchronous spike-and-wave discharges (SWD) in the electroencephalogram (EEG).

Wistar Albino Glaxo Rijswijk (WAG/Rij) rats are a widely used experimental model of absence epilepsy. EEG recordings in WAG/Rij indicate occasional SWDs consisting of bursts lasting about 6 seconds with a frequency of 9 Hz. The potency of antiepileptic treatments is typically assessed in WAG/Rij by monitoring the changes in SWD occurrence using long telemetric recordings as well as tedious sleep-cycle analysis.

Here we aimed to investigate acutely the brain excitability changes in WAG/Rij during standardized deep anesthesia. A burst-suppression (BS) EEG pattern induced by isoflurane at a suppression ratio of 40-80%, abolished the occurrence of SWDs. Nevertheless, BS reactivity, assessed as the reduction in suppression ratio that occurred during intermittent photic stimulation (2 seconds interstimulus interval) for 1 minute, was increased in WAG/Rij rats as compared to age-matched Wistar rat controls. The BS reactivity of WAG/Ri was reduced after ethosuximide and paradoxically increased after carbamazepine at doses that had no effect on controls.

Our data suggest that the BS reactivity could be used as a translational outcome measure in epilepsy treatment studies.

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ASSESSMENT OF THE RAT POST-ISCHEMIC BRAIN BY BURST-SUPPRESSION EEG REACTIVITY

Laurentiu Tofan[1], Alexandru-Catalin Paslaru[1], Mihai Stancu[1], Bogdan Pavel[1], Denise Mihaela Zahiu[1], Alexandru Calin[3], Ana-Maria Zagrean[1], Leon Zagrean[1], Mihai Moldovan[1,2]

1Physiology and Fundamental Neuroscience, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania;
2Department of Neuroscience, University of Copenhagen, Copenhagen, Denmark;
3Department of Pharmacology, Oxford University, Oxford, United Kingdom

laurentiud.tofan@gmail.com

EEG assessment of diffuse ischemic brain injury remains methodologically challenging. We reported that in comatose patients with „burst-suppression" (BS) EEG, the decrease in suppression ratio during visual stimulation, referred to as BS reactivity, correlated with injury severity. A reversible BS state can be induced by deep general anesthesia. The aim of this study was to assess the anesthetic BS reactivity to photic stimulation following experimental global cerebral ischemia (GCI).

Adult male Wistar rats accommodated to a 12 h dark/night cycle were subjected to a 5-minute GCI by „4-vessel occlusion".

Continuous telemetric EEG/EMG monitoring within 48 hours of reperfusion indicated no seizures, or abnormal slowing of resting EEG rhythms. Sleep-wake cycles recovered, showing only an attenuated nocturnal increase in wakefulness, consistent with reduced nocturnal activity levels measured by video-tracking. EEG investigations under anesthesia did not detect abnormalities in visual evoked potentials. Nevertheless, reactivity of anesthetic BS patterns measured over 1 min, was only half than in controls due to increased accommodation to stimulation. By convoluting an alpha function with the binary BS signal and optimizing the function time constant, we found that after GCI there was an increased time-to peak from 3 to 7 sec. A similar delay was observed in the peak of the hemodynamic response function, measured by burst-triggered averaging of the laser-doppler signal recorded over 30 minutes.

Our data suggest that the impaired BS reactivity reflects a global impairment in vascular reactivity which could be used in neuroprotection studies.

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THE EFFECT OF 5-HTTLPR ALLELIC POLYMORPHISM ON EEG REACTIONS IN STOP-SIGNAL PARADIGM BETWEEN DIFFERENT ETHNIC GROUPS

Alexander Savostyanov, Darya Basovkina, Alexandra Karpova, Nataliya Borisova, Alexander Saprygin, Andrey Bocharov, Gennady Knyazev

Institute of Cytology and Genetics SB RAS, State Research Institute of Physiology and Basic Medicine, Novosibirsk, Russia; North-Eastern Federal University, Yakutsk, Russia.

Alexander.Savostyanov@gmail.com

Stop-signal paradigm (SSP) is an experimental approach for the checking of human ability for motor control. In SSP-experiment, a subject should press button after a target stimuli onset or suppress already prepared motion after stop-signal onset. The serotonin transporter (5-HTT) is a genetic marker of individual variation in serotoninergic function. The promoter region of the 5-HTTLPR contains short (S) and long (L) variants. The aim of study is an exploration of the 5-HTTLPR effects on a motor control abilities of people among different ethnic groups.

486 people from different regions of Siberia (Novosibirsk region, Tyva and Yakutia) participated in the SSP-experiment. DNA for 5-HTTLPR identification was extracted from buccal cells. EEG was registered via 64 or 128 channels by means of the actiChamp amplifier, by Brain Products, Germany. Event-related spectral perturbations were used as a measure of task-induced brain activity.

Results: S- and L- alleles had different distributions among Caucasoid and Mongoloid populations. SS genotype was associated with better motor control in SSP than LL and LS genotypes. In EEG, people with LL genotype showed longer alpha-desynchronization in comparison with SS-carriers. People with LS, who are constantly living in urban conditions, demonstrated EEG and behavioral patterns similar with LL-carriers, whereas LS-carriers from rural regions showed high similarities with SS-carriers.

Conclusion: 5-HTTLPR polymorphism is associated with ability for motor control, but this association is modulated by the environmental factors. Study is supported by grant of RFBR N18-29-13027. Data collection in Yakutiya is supported by grant of RFBR N18-415-140021.

P131

EFFECT OF CHRONIC FLUOXETINE ADMINISTRATION ON BEHAVIOR AND BRAIN MRNA LEVEL OF BDNF AND 5-HT1A RECEPTOR GENES IN MOUSE LINES DIFFERED BY 5-HT1A RECEPTOR FUNCTION

Kondaurova E.M., Rodnyy A.Ya., Naumenko V.S., Popova N.K.

Department of Behavioral Neurogenomics, Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russia

chudabest@gmail.com

Recombinant B6.CBA-D13Mit76C mouse line is characterized by increase in postsynaptic and decrease in presynaptic functional responses mediated by 5-HT1A receptor compared to control B6.CBA-D13Mit76B mouse line. The B6.CBA-D13Mit76C mice has decreased 5-HT metabolism and increased BDNF/proBDNF ratio in hippocampus.

The aim of the present study was to evaluate the effect of chronic fluoxetine administration (20mg/kg, 14 days i.p.) on mobility in Forced swim test (FST) and on mRNA levels of *bdnf* and *5-HT1A receptor* genes using real time PCR in the brain of B6.CBA-D13Mit76B and B6.CBA-D13Mit76C mice. The data were analyzed using two-way ANOVA followed by Fisher's LSD test.

Chronic fluoxetine treatment decreased mobility in FST of the B6.CBA-D13Mit76C ($p<0.05$) but not in the B6.CBA-D13Mit76B. mRNA levels for *bdnf* and *5-HT1A receptor* genes in midbrain of the control and fluoxetine-treated groups did not differ in both lines. However, the mRNA level of *5-HT1A receptor* gene was decreased ($p<0.01$) in the cortex and in the hippocampus ($p<0.01$) of B6.CBA-D13Mit76C but not B6.CBA-D13Mit76B mice treated with fluoxetine. The mRNA level of *bdnf* gene was increased in the hippocampus of B6.CBA-D13Mit76C ($p<0.05$) treated with fluoxetine.

Thus, chronic administration of fluoxetine increased depressive-like behavior, decreased mRNA level for postsynaptic but not presynaptic *5-HT1A receptor* and increased mRNA level for *bdnf* gene in hippocampus of B6.CBA-D13Mit76C mice.

Animal maintenance was supported by basic research project # 0324-2019-0041;

The work was supported by RSF # 17-15-01021.

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TAURINE EFFECTS ON LINDANE-INDUCED GENERALIZED SEIZURES IN RATS: ELECTROENCEPHALOGRAM AND CONVULSIVE BEHAVIOR ANALYSIS

Ademović Anida[1], Radišić Vanja[1], Leković Aleksa[1], Grubač Željko[1], Šutulović Nikola[2], Rašić Marković Aleksandra[2], Stanojlović Olivera[2], Hrnčić Dragan[2]

1Faculty of Medicine, University of Belgrade, Serbia;
2Institute for Medical Physiology „Rihard Burian", Faculty of Medicine, University of Belgrade, Serbia

anidaa94@yahoo.com

Introduction: Epilepsy has been standing for a very common neurological disorder. Taurine is neuromodulator with a variety of physiological roles and controversial and still not clear role in epileptogenesis. Lindane can provoke tonic-clonic generalized epileptic seizure in experimental animals with the well-defined alterations in electroencephalogram (EEG), leading to the specific convulsive behavior.

Aim: of this study was to examine effects of taurine on both EEG parameters and convulsive parameters upon lindane-induced generalized seizures in rats.

Material and methods: Experiment was conducted on Wistar albino male rats randomly assigned to control (dimethylsulfoxide (DMSO),0,5 ml/kg,n=8), taurine (T, taurine 150 mg/kg,n=8), lindane (L, lindane in convulsive dose of 8 mg/kg,n=8) and T+L(taurine 150 mg/kg applied 30 min prior to lindane,n=8). Upon drug administration, convulsive behavior was assessed for 30 minutes by using descriptive rating scale (grade 1-4). The main EEG characteristics, such as number and duration of ictal period, as well as the seizure latency period were measured and further analyzed.

Results: Control group, including DMSO and T group, did not develop any sign of convulsive behavior. T+L group developed less seizures and they were with the lower gradus compared to L group. Additionally, the latency of seizures in T+L was significantly longer than in L group. This was corroborated by the EEG analysis where number and duration of ictal periods was lower than in L group.

Conclusion: We have shown that taurine has an antiepileptic effect on the generalized seizures induced by lindane in rats.

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P133

SHORT-TERM FASTING INCREASES INSULIN AND PHOSPHORYLATED ERK1/2 CONTENT IN RAT HYPOTHALAMUS

Tamara Dakic, Tanja Jevdjovic, Iva Lakic, Jelena Djordjevic and Predrag Vujovic

Department for Comparative Physiology and Ecophysiology, Institute for Physiology and Biochemistry, Faculty of Biology, University of Belgrade, Belgrade, Serbia

tamara.dakic@bio.bg.ac.rs

Aims: Fasting is a condition characterized by the absence of food intake and therefore may represent a disturbance to energy homoeostasis. Insulin regulates numerous processes in the brain including feeding behavior, glucose metabolism and energy homeostasis. The aim of this study was to examine effect of six-hour fasting on insulin expression and signaling in the rat hypothalamus.

Methods: Insulin mRNA expression was assessed by qPCR. The amount of insulin receptor (IR), insulin receptor substrate (IRS) 1 and 2, PI3K, AKT1/2/3, mTOR1 Ser/Thr kinase, ERK1/2 and their phosphorylated forms (pIRTyr1361, pIRS1Tyr612, pIRS2Ser731,pAKT1/2/3Ser473, pmTORSer2448, pERK1/2Thr202/Tyr204) was measured by immunoblotting. Hypothalamic distribution of insulin and p-IRTyr1361 was determined by immunofluorescence.

Results: After short-term fasting insulin mRNA expression and protein content in the hypothalamus were increased. Insulin immunopositivity was detected in the NeuN-positive cells of periventricular nucleus (PeV). Phospho-IRTyr1361 immunoreactivity was detected in the same region. The amount of both IR and pIRTyr1361 were increased while the levels of IRS1, 2 and their phosphorylated forms were not altered. The content of total and activated PI3K, AKT1/2/3, mTOR remained unchanged. Lastly, amount of total ERK1/2 was unchanged in fasting rats, while pERK1/2Thr202/Tyr204 was increased.

Conclusion: Results showed that short-term fasting promoted hypothalamic insulin production and led to the activation of insulin receptor in the PeV. Despite activation of IR, no differences in PI3K/AKT signaling pathway activation were observed. The fact that increased amount of activated ERK1/2 was detected, indicates that locally produced insulin may potentially be involved in regulation of genes expression important for cell growth and differentiation.

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THE MODULATORY ROLE OF SUBCHRONIC EXERCISE ON ANXIETY-LIKE BEHAVIOUR IN FEMALE RATS

Djuric E[1], Škrijelj D[1], ŠutulovićN[1], Grubač Z[1], Puškaš N[2], Zaletel I[2], Nikolić T[3], Petronijević N[3], Hrnčić D[1], Macut Dj[4], Stanojlović O[1], Rašić-Marković A[1]

1Institute of Medical Physiology "Richard Burian", School of Medicine, University of Belgrade, Belgrade, Serbia;
2Institute of Histology and Embryology, School of Medicine, University of Belgrade, Belgrade, Serbia;
3Institute of Clinical and Medical Biochemistry, School of Medicine, University of Belgrade, Belgrade, Serbia;
4Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, Belgrade, Serbia

emilijarandom1@gmail.com

Aim: Numerous studies indorse beneficial effect of exercise on brain and mental health. Role of exercise on anxiety is still unclear. A growing body of evidence suggest anxiolytic effect, opposing to others that suggest anxiogenic or no effect in rodent models. Hence the aim of our study was to investigate the effect of subchronic aerobic exercise on anxiety-like behaviour, neuropeptide Y (NPY+) and parvalbumine (PV+) expression in the hippocampus and hormonal levels.

Methods: Adult female Wistar rats have been divided into sedentary control (C) and exercise (E) group. E group ran 30 min daily on a treadmill for 15 consecutive days. Locomotor and exploratory activity have been tested in automated Open Field chamber. Independent measures included total ambulation distance (cm), center ambulation distance (cm) and time (s), periphery ambulation distance (cm) and time (s), number of rearings and thigmotaxis index. The number of PV+ and NPY+ immunoreactive cells in the hippocampus was determined immunohistochemically. Serum levels of corticosterone, progesterone, estradiol and testosterone were determined by commercial ELISA kits.

Results: Running rats have shown decreased total ambulation distance and number of rearings. Exercise significantly decreased number of NPY+ and PV+ interneurons in CA1 section, and increased estradiol levels.

Conclusion: Based on the presented data, it can be concluded that subchronic exercise induces anxiety-like behavior in female rats which correlates with decreased NPY+ and PV+ expression in CA1 region of the hippocampus. Discrepancy between studies is likely due to different length, modality of exercise and gender, therefore further research is needed.

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CHRONIC SLEEP FRAGMENTATION AFFECTS LINDANE-INDUCED SEIZURES: THE ROLE OF PROINFLAMMATORY INTERLEUKINS

Željko Grubač[1], Nikola Šutulović[1], Đurđa Jerotić[2], Sonja Šuvakov[2], Nemanja Useinović[1], Aleksandra Rašić-Marković[1], Đuro Macut[3], Tatjana Simić[2], Olivera Stanojlović[1], Dragan Hrnčić[1]

1Laboratory of Neurophysiology, Institute of Medical Physiology "Richard Burian", Belgrade University Faculty of Medicine, Belgrade, Serbia;
2Institute of Medical and Clinical Biochemistry, Belgrade University Faculty of Medicine, Belgrade, Serbia;
3Clinic of Endocrinology, Diabetes and Metabolic Disease, CCS, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

zeg18@hotmail.com

Introduction: Hyperexcitability in sleep apnea is believed to be provoked by hypoxemia, but sleep fragmentation can also play a significant role. Sleep fragmentation can trigger inflammatory mechanisms. The aim was to investigate the effects of chronic sleep fragmentation on seizure susceptibility and brain cytokine profile.

Methods: Chronic sleep fragmentation in rats with implanted EEG electrodes was achieved by treadmill method. Rats were randomized to: 1) treadmill control (TC, only OFF mode); 2) activity control (AC, 10min ON and 30min OFF) and 3) sleep fragmentation (SF, 30s ON and 90s OFF) group. Convulsive behavior was assessed 14 days later by seizure incidence, latency time and seizure severity during 30 min upon lindane (4 mg/kg, ip.). Number and duration of EEG ictal periods were determined. IL-1β and IL-6 were measured in the hippocampus, thalamus and cerebral cortex in rat cohort that underwent the same protocol.

Results: Incidence and severity of seizures were significantly increased, latency significantly decreased in SF compared with TC group. Seizure latency was also significantly decreased in SF compared to AC group. Number of ictal periods were increased and its duration presented tendency to increase in SF comparing to AC group. IL-1β was significantly increased in the thalamus, cortex and hippocampus in SF compared to AC and TC group. Il-6 was statistically higher only in cortex of SF animals, while in thalamic or hypocampal tissue no difference was observed between groups.

Conclusion: Fourteen days sleep fragmentation increases seizure susceptibility in rats and modulates brain production of IL1β and IL6.

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DIFFERENTIAL EFFECTS OF URB 597, A SELECTIVE INHIBITOR OF FATTY ACID AMIDE HYDROLASE, ON NORADRENALINE TURNOVER IN PREFRONTAL CORTEX AND HIPPOCAMPUS OF CHRONICALLY STRESSED RATS

Milica Jankovic, Harisa Ferizovic, Natasa Spasojevic, Bojana Stefanovic, Sladjana Dronjak

Institute of Nuclear Sciences "Vinča", Laboratory of Molecular Biology and Endocrinology, University of Belgrade, Belgrade, Serbia

milicajankovic2003@yahoo.com

Aims: The complex nature of depression is mirrored by the difficulties in treating it successfully. Evidence for the role of endocannabinoid system in the depression and anxiety disorders is starting to emerge, making it attractive target for potential therapy. In this study we examined the effects of URB597, a selective inhibitor of fatty acid amide hydrolase, on noradrenaline (NA) content and turnover in rat prefrontal cortex (PFC) and hippocampus (HC).

Methods: Wistar rats, 11 weeks old, were subjected to chronic unpredictable stress (CUS) for 6 weeks. In the last 2 weeks rats received daily either URB597 (0.3 mg/kg/day, i.p.) or vehicle. NA content was determinated using HPLC method. Western blot was used for assessing the levels of the noradrenaline transporter (NET), enzymes responsible for noradrenaline synthesis (tyrosine hydroxylase, TH and dopamine-beta-hydroxylase, DBH) and degradation (monoamine oxidase A, MAO-A and catechol-O-methyltransferase, COMT).

Results: Our findings showed significant decrease of NA content in both PFC and HC of stressed rats compared with control animals. There was a significant decrease in synthesis while there was an increase in NA degradation in both structures. URB597 treatment improved noradrenaline content in PFC and recovered levels of DBH and MAO-A which were affected by chronic stress. However, it had little or no effect in hippocampus.

Conclusions: These results suggested that URB597 may exert its therapeutic effect primarily by normalizing a disrupted PFC activity.

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CONTINUOUS GNRH TREATMENT BLOCKS BASAL FSHB BUT NOT LHB EXPRESSION IN RAT PITUITARY GONADOTROPHS

Marija M. Janjic[1,2], Rafael Maso Previde[1], Kosara Smiljanic[1], Patrick A. Fletcher[3], Arthur Sherman[3], Ivana Bjelobaba[1,2], and Stanko S. Stojilkovic[1]

1Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892, USA; 2Institute for Biological Research Sinisa Stankovic, University of Belgrade, 11000 Belgrade, Serbia, and 3Laboratory of Biological Modeling, National Institute of Diabetes, Digestive and Kidney Diseases, NIH, Bethesda, MD 20892, USA

marija.janjic@ibiss.bg.ac.rs

Aim: To investigate mechanisms of inhibition of reproductive functions by continuous GnRH application, with focus on gonadotropin gene expression and secretion.

Methods: Experiments were performed in vivo and in vitro using female and male rats and cultured pituitary cells. Gene expression was characterized by qRT-PCR analysis. For this purpose, we searched for an appropriate reference gene. Protein expression was characterized by immunocytochemistry, and ELISA and Western blot analyses were used for LH measurements.

Results: Continuous exposure of pituitary cells in static cultures to Gnrh agonists induced a prolonged blockade of Fshb expression after a brief stimulation. However, only a minor and transient inhibitory effect on Lhb expression was detected. Such Lhb profile probably reflects the expression status of three genes controlling Lhb transcription during the treatment: stimulation of Egr1, inhibition of Nr5a1, and no effect on Pitx1 expression. In contrast, continuous Gnrh treatment stimulated Lh secretion in static cultures, leading to depletion of the secretory pool. In vivo administration of a Gnrh agonist was also accompanied with a rapid increase in serum Lh levels and a progressive depletion of the intrapituitary Lh levels without major effects on Lhb expression.

Conclusion: Blockade of Fshb expression and depletion of the Lh secretory pool are two major factors accounting for weakening of the gonadotroph secretory function during continuous Gnrh treatment.

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APPLICATION OF HYPERBARIC OXYGEN AFTER EXPERIMENTAL BRAIN INJURY PROMOTES MACROPHAGES TRANSITION FROM PRO-INFLAMMATORY M1 TO ANTI-INFLAMMATORY M2 PHENOTYPE

Jeremic R[1], Brkic P[1], Dacic S[2], Djelic M[1], Pekovic S[3]

1Institute of Medical Physiology "Richard Burian", Faculty of Medicine, University of Belgrade, Belgrade, Serbia;
2Institute of Physiology and Biochemistry, Faculty of Biology, University of Belgrade, Belgrade, Serbia;
3Department of Neurobiology, Institute for Biological Research "Sinisa Stankovic", University of Belgrade, Belgrade, Serbia

rdjeremic@yahoo.com

Microglial activation is a pathological hallmark of traumatic brain injury (TBI). Following TBI, activated microglia/macrophages adopt different phenotypes, generally categorized as M-1, or pro-inflammatory phenotype that is detrimental to recovery, and M-2, or anti-inflammatory phenotype, which aids in brain repair. The aim of present study was to investigate the effects of treatment with hyperbaric oxygen (HBOT) on microglia M1/M2 polarization after TBI in rats.

The TBI in male Wistar albino rats was induced by sensorimotor cortex ablation (SCA). The coordinates were: 2 mm anterior and 4 mm posterior to bregma, and 4 mm lateral from the midline. SCA was performed by suction to the depth of white matter. HBOT protocol: pressure applied 2.5 absolute atmospheres (ATA), 60 minutes, once daily for 10 days. Effects of HBOT were monitored using double immunofluorescence staining with specific markers: ED1 (marker of activated microglia/macrophages), TNF-α (Tumor necrosis factor-α, marker of M1 pro-inflammatory phenotype), IL-10 (Interleukin-10) and arginase-1 (ARG-1) as markers of M2 anti-inflammatory macrophages.

Treatment with HBO decreases a huge number of activated ED1+/TNF-α+ M1 macrophages seen in the perilesioned cortex after SCA. In contrast, HBOT significantly amplified the number of ED1+/IL-10+/ARG-1+ M2 anti-inflammatory macrophages in the injured cortex, and thereby shifts M1/M2 polarization towards M2 phenotype.

Our findings indicate that HBOT decreases the number of M1 and increases number of M2 microglia/macrophages around and within the lesion site, thus contributing to the resolution of inflammation, promoting of neuroprotection and therefore could be a useful treatment for the suppression of neuroinflammation after brain injury.

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SINGLE SESSION NEUROFEEDBACK TREATMENT ALTERS THETA/BETA-1 AND THETA/ALPHA RATIOS BUT NOT SUFFICIENT TO INDUCE CLINICAL ENHANCEMENT IN ATTENTION

Kesić S[1], Yadollahpour A[2], Riahi F[3], Naraghi M[2], Stojadinović G[1], Spasić S[4,5]

1Department of Neurophysiology, Institute for Biological Research "Siniša Stanković," University of Belgrade, Belgrade, Serbia;
2Department of Medical Physics, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran ;
3Department of Psychiatry, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran;
4Department of Life Sciences, Institute for Multidisciplinary Research, University of Belgrade, Belgrade, Serbia ;
5Singidunum University, Faculty of Informatics and Computing, Belgrade, Serbia

yadollahpour.a@gmail.com

Background and Aims: This study investigated the effects of single session neurofeedback treatment (NFT) on attention in healthy individuals performing a visual attention task.

Methods: This was an open-label single-blinded trial conducted on 14 healthy university students (n=14; mean=23.35±0.58 years) of a major medical university in Iran. The subjects underwent a single session NFT while performing attentional network task (ANT). The NFT protocol was theta suppression/beta-1enhancement applied at Cz for 20 min. Before and immediately after NFT, EEG signals were recorded in subjects while performing ANT. EEGs were recorded using a 19 channel device and 10-20 placement protocol.

Results: The single session NFT increased the theta/beta-1 ratio in most of the electrode sites, and the increase was statistically significant compared to the pre-intervention in the T6 site ($p=0.011$). The ratio decreased in just three sites of C3, Fz, and Cz, of them Fz showed a significant reduction ($p=0.026$). Contrary, the theta/alpha ratio decreased in most of the electrodes where the reductions were statistically significant in P3, P4, Cz, Pz ($p<0.05$), and C3 ($p<0.01$). The F7, F8, T3, and T4 showed no significant increased theta/alpha ratio. The central, temporal, and occipital regions were involved in the NFT induced changes. Single NFT did not significantly change alerting, executive, or orienting networks of ANT.

Conclusions: Theta/beta-1 and theta/alpha ratios can be reliably used to assess NFT induced attention enhancement. However, single NFT did not induce clinical outcomes, and repeated sessions seem necessary to modulate alerting, executive, or orienting networks of ANT.

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IRON MODULATES NOREPINEPHRINE EFFECT ON ASTROCYTES

Jelena Korać[1], Ljiljana Nikolić[2], Dunja Bijelić[3], Ivan Spasojević[1], Jelena Bogdanović Pristov[1]

1Department of Life Sciences, Institute for Multidisciplinary Research, University of Belgrade, Serbia;
2Institute for Biological Research "Siniša Stanković", University of Belgrade, Serbia;
3Center for Laser Microscopy, Faculty of Biology, University of Belgrade, Serbia

jskorac@gmail.com

Aims: Astrocyte position between synapses and blood vessels allows them to fulfil crucial functions such as regulation of synaptic activity and potassium buffering. Well positioned in the close vicinity of synaptic cleft astrocytes are considered to be a direct target of norepinephrine (NE). Synaptic activity and neurotransmitter actions can be influenced by extracellular iron. Here we investigated whether iron interacts with NE and if this interaction can modulate astrocyte response to NE.

Methods: To investigate the interaction between iron and norepinephrine we used spectrophotometry approach. Iron effect on astrocyte response to NE was examined by the whole-cell patch-clamp technique. Membrane currents were recorded from cultured cortical astrocytes prepared from WT rats.

Results: Using spectrophotometry we observed that iron interacts with NE which leads to the formation of a stable complex in the 1:1 stoichiometry. We also found that iron bound to NE completely blocks NE-induced increase of large-conductance calcium sensitive potassium current in astrocytes.

Conclusions: Astrocyte response to NE is modified when this neurotransmitter forms a complex with iron. This implies that NE binding to astrocytic noradrenergic receptors may be prevented by iron. Our findings point toward compromised astrocyte functions related to the potassium buffering when NE action is modified by iron.

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NEUROBEHAVIOURAL PERFORMANCE IN OPEN FIELD TEST IN MICE WHICH WERE EXPOSED PRENATALLY TO DIFFERENT DOSES OF LEVETIRACETAM

Podgorac J, Petković B, Stojadinović G, Martać Lj, Pešić V

Institute for Biological Research „Siniša Stanković", University of Belgrade, Serbia

jelenapodgorac@yahoo.com

Introduction: Levetiracetam (LEV) represent a relatively new-age drug, which is firstly recommended as adjunctive therapy for focal seizures, secondly for the treatment of generalized tonic-clonic epilepsy and juvenile myoclonic epilepsy. Recently, it has been introduced as initial monotherapy (Abou-Khalil, 2008), in EU since 2006 (Stephen et al, 2011). Antiepileptic therapy during pregnancy with LEV takes a special place as regarding pregnancy risk categories LEV belongs to pregnancy category C.

Aim: Our aim was to determine, in animal model, neurobehavioral developmental disorder of young, without body malformations, which mothers were treated with different doses of levetiracetam during whole gestation. Open field test was used to assess general locomotor, stereotypic and vertical activity in mice.

Materials and Methods: Study was consisted of four groups, three experimental and control one. Adult female NMRI mice were treated with subcutaneous injection of LEV in doses of 158mg/kg/day, 211mg/kg/day, 316mg/kg/day and control group with saline, during breeding and whole gestation. We investigated locomotor and exploratory activity in open field test at 45th day of postnatal life, using parameters such as horizontal distance, rearing, spatial preferences and grooming activity.

Results: Neurobehavioral parameters were analyzed using the Kruskal-Wallis-test. Between experimental groups (158mg/kg/day, 211mg/kg/day and 316mg/kg/day) and control group was found significant differences.

Conclusion: Test for neurobehavioral assessment of offspring was conducted at 45th postnatal day, which correspond to adolescent period of humans. Neurobehavioral parameters show different quality of postnatal development in treated groups compared to control group.

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INCREASED SEIZURE SUSCEPTIBILITY IN FEMALE OFFSPRING AFTER PRENATAL ANDROGENIZATION MAY CORRELATE TO INCREASED EXPRESSION OF BDNF IN THE HIPPOCAMPUS

Rankov Petrovic B[1], Škrijelj D[1], Djurić E[1], Šutulović N[1], Jovanović Dj[2], Šuvakov S[2], Simić T[2], Hrnčić D[1], Stanojlović O[1], Rašić-Marković A[1]

1Institute of Medical Physiology "Richard Burian", School of Medicine, University of Belgrade, Belgrade, Serbia;
2Institute of Clinical and Medical Biochemistry, School of Medicine, University of Belgrade, Belgrade, Serbia

bojana@srbn.com

Aims: Prenatal manipulations with gonadal hormones have powerful influences on brain development and behaviour of the offspring. The aim of our study was to examine the effect of prenatal androgenization on seizure susceptibility, hippocampal expression of Ki67+ and NeuN+ cells and the level of precursor and mature form of the brain derived neurotrophic factor (proBDNF and mBDNF, respectively) in the hippocampus and cerebral cortex.

Methods: Pregnant female Wistar albino rats were divided into two groups: testosterone treated (T) and control (C) dams. In order to examine behavioral characteristics of seizures, adult female offspring of T and C dams was treated either with homocysteine-thiolactone 5.5 mmol/kg (Th and Ch group); or with 0.9% NaCl (Ch and Cc groups). Seizure behavior was assessed by latency, incidence, number and intensity of seizure episodes. The number of NeuN+ and Ki67+ immunoreactive cells in the hippocampus was determined immunohistochemically. The level of proBDNF and mBDNF expression in the hippocampus and cerebral cortex was analyzed with the Western blot test.

Results: Prenatal androgenization increased seizure susceptibility in adult female offspring: seizure latency was significantly shorter, and the number of seizure episodes was significantly higher in Th group. NeuN immunoreactivity in the hippocampus was higher Tc group, as well as the level of proBDNF, while mBDNF was higher both in the hippocampus and the cortex of Tc group in comparison with the Cc group.

Conclusions: Increased seizure susceptibility in adult female offspring prenatally treated with testosterone positively correlates with increased number of NeuN and increased levels of proBDNF and mBDNF in the hippocampus.

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NEUROTOXIC EFFECTS OF 2,4-DIAMINOBUTYRIC ACID ON LEECH RETZIUS NEURONS

Svetolik Spasić[1], Marija Stanojević[1], Vladimir Nedeljkov[1], Milica Prostran[2], Srđan Lopičić[1]

1Institute for Pathophysiology "Ljubodrag Buba Mihailović", Faculty of Medicine, University of Belgrade, Serbia;
2Institute for Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Belgrade, Serbia

svetolikspasic@gmail.com

Aim: Neurotoxic effects of 2,4 – diaminobutyric acid (DABA) were first demonstrated upon its isolation from Lathyrus seeds – cause of human neurolathyrism. It was later shown that ubiquitous Cyanobacteria produce this non-protein amino acid, raising concerns about global human exposure. As mechanisms of neurotoxicity of DABA were never completely explained, we investigated its effects on the cell membrane potential of leech Retzius neurons.

Method: Classical intracellular recordings using glass microelectrodes were performed. DABA was administered in concentrations of 1, 3, 5 and 10 mM over 3 minutes. Input membrane resistance was measured using current clamp technique by injecting hyperpolarizing current pulses through the recording electrode.

Results: Application of 1mM DABA depolarized membrane potential by 5.01±0.43 mV (n=6, $p<0.01$), while 3 mM DABA produced depolarization of 9.84±1.38 mV (n=7, $p<0.01$). Rapid depolarization of membrane potential by 39.63±2.22 mV (n=9, $p<0.01$) was induced by 5 mM DABA, and administration of 10 mM DABA caused membrane depolarization of 47.05±4.33 mV (n=6, $p<0.01$). After washout, cells exposed to 1 or 3 mM DABA fully recovered, only half of the cells treated with 5 mM DABA showed recovery and none of the cells recovered upon application of 10 mM DABA. Applied in concentration of 5mM, DABA induced a decrease of the input membrane resistance by 8.09±1.51 MΩ (n=7, $p<0.01$).

Conclusion: DABA induces substantial concentration-dependent membrane depolarization and, at higher concentrations, irreversible functional changes of neurons, confirming its neurotoxic potential. Decrease of input membrane resistance indicates that this effect is a consequence of increased membrane permeability.

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CAN CHRONIC PELVIC PAIN PROVOKE RATS BRAIN HYPEREXCITABILITY?

Nikola Šutulović[1], Željko Grubač[1], Anida Ademović[1], Božo Knežević[1], Nela Puškaš[2], Aleksandra Rašić-Marković[1], Olivera Stanojlović[1], Dragan Hrnčić[1]

1Laboratory of Neurophysiology, Institute of Medical Physiology "Richard Burian", Belgrade University Faculty of Medicine, Belgrade, Serbia ; 2Institute of Histology and Embryology "Aleksandar Dj. Kostic", Belgrade University Faculty of Medicine, Belgrade, Serbia

nikolasutulovic@gmail.com

Introduction: Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) has growing overall prevalence as high as 35%. Antiepileptic medications are potent in the CP/CPPS treatment. There are clinical evidences on relationship between epilepsy and urological disorders, but without proper investigation in experimental models. The aim of this study was to investigate brain excitability in rats with experimentally induced CP/CPPS.

Methods: Adult male Wistar albino rats (n=16) were divided into: CP/CPPS (intraprostatic injection of 3% λ-carrageenan) and SHAM (0.9% NaCl) group. Mechanical pain thresholds in the scrotal skin were determined by electrical von Frey aesthesiometer prior to, as well as, 48h, 72h and 7d upon injection. Seventh day upon intraprostatic injection, we challenged rats with subconvulsive dose of lindane (4 mg/kg). Hereupon, we assessed rats convulsive behavior (seizure incidence, latency and severity) and EEG manifestations (number and duration of ictal periods). After the test, the prostates were removed for histological evaluation (hematoxylin-eosin).

Results: Scrotal pain threshold was significantly decreased in CP/CPPS animals compared to SHAM animals ($p<0.01$). Experimental animals revealed significantly higher incidence ($p<0.05$), decreased latency time ($p<0.05$) and augmented severity ($p<0.05$) of lindane-induced seizures compared to control. EEG analysis showed increased number of ictal periods ($p<0.05$) in CP/CPPS rats, with no statistically significant difference in the duration of EEG ictal periods. Histological evaluation demonstrated nonbacterial prostate inflammation with leukocyte infiltration in CP/CPPS animals compared to unaltered prostate histology in Sham animals.

Conclusions: Animals with experimentally induced CP/CPPS showed higher brain excitability and were more prone to lindane-induced seizures.

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BIOTIC PATTERNS IN THE EEG AND EKG SIGNAL DURING ISOPRENALINE INDUCED ACUTE MYOCARDIAL INFARCTION IN RATS

Marko Vorkapić[1], Milica Janković[2], Andrej Savić[2,3], Nemanja Useinović[1], Aleksandra Rašić-Marković[1], Olivera Stanojlović[1], Dragan Hrnčić[1]

1Institute of Medical Physiology "Richard Burian", Faculty of Medicine, University of Belgrade, Serbia ;
2University of Belgrade – School of Electrical Engineering, Serbia;
3Tecnalia Serbia Ltd., Belgrade, Serbia

markovorx@gmail.com

Aim: Biotic signals are defined as nonlinear biological signals different from stochastic, chaotic and periodic signals which can be described by recursive process equations that have bipolar feedback (mathematical bios). We have previously shown the utility of EEG biotic characteristics during lindane induced epilepsy. The EEG and EKG are known as the prototypical biotic signal but their behavior during acute myocardial infarction (AMI) has not yet been established.. Our goal was to determine EEG spectral density changes, as well as EKG biotic parameter changes- entropy and series isometry - in isoprenaline induced AMI in rats

Methods: We used adult Wistar albino rats that had two holter electrodes fixed to the back connected to the EKG and scalp electrodes for EEG. Acquisition lasted 60 min before and 240 min after isoprenaline administration (150 mg/kg, i.p) and for one hour after 24 hours. The signal was cut into 1 hour intervals. Offline analyses of acquired EEG and EKG signals were done by Bios Analyzer and NeuroSciLab software (custom made signal analysis programs).

Results: All epochs recorded after isoprenaline administration showed a statistically significant decline in entropy and increase in isometry measures of the EKG compared to baseline. There were changes in spectral characteristics of the EEG signal. There were no statistically significant changes between baseline EEG or EKG recordings compared to recordings made after 24 hours.

Conclusions: We have shown that biotic parameters such as entropy and series isometry are sensitive to changes occurring during isoprenaline induced AMI. Further quantification of these changes and comparison with more common EKG analysis parameters is needed for better understanding their practical implications.

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RAT VENTRAL CAUDAL NERVE: A QUANTITATIVE MORPHOMETRIC STUDY

Zuzana Dzurjaškova, Juraj Blaško, Ivo Vanicky

Institute of Neurobiology, Biomedical Research of Center, Slovak Academy of Sciences, Košice, Slovakia

dzurjaskova@saske.sk

Ventral caudal nerve is probably the longest peripheral nerve in a rat body. Therefore, we intend to use it as a model nerve for long-distance regeneration studies. Detailed knowledge on nerve morphology is necessary for the quantitative evaluation of regeneration success or failure in nerve transection and repair experiments. The present study therefore seeks to systematize the morphology and some morphometrical parameters of the ventral caudal nerve in Wistar albino rats.

Seven male rats (b.w. >250 g) were deeply anesthetized and under operating microscope, the whole trunk of their ventral caudal nerve was dissected and removed. The stretched nerve was then immersion-fixed in 2.5% glutaraldehyde in 0.1 PB. The whole specimen was embedded into protein matrix that facilitated its systematic precise cutting into 1mm thick transversal slabs. The slabs were postfixed in 1% osmium tetroxide and embedded into epoxy resin. A series of samples from every 10th millimeter were collected, and 1µm thick transversal sections were prepared for further morphometric analysis. On every section, axon counting was performed with aid of NeuroCounter software, which reflects the total number of axons as well as several parameters of each axon (area, diameter, circularity etc.). The g-ratio of ventral caudal nerves was evaluated by ImageJ software and gathered data closely correspond to theoretical predictions.

Our morphometric analyses describe several parameters of the intact ventral caudal nerve, and their changes along the rostrocaudal axis of the nerve.

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EVALUATION OF CYTOTOXIC AND GENOTOXIC EFFECTS OF OPTIMIZED WIRELESS ENERGY TRANSFER SYSTEM ON HUMAN NEURAL CELLS

Tóthová B[1], Škovierová H[1], Okajčeková T[1,2], Pavelek M[3], Špánik P[3], Frivaldský M[2] and Halašová E[1,4]

1Biomedical Center Martin, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Slovakia;
2Department of Medical Biochemistry, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Slovakia;
3Department of Mechatronics and Electronics, Faculty of Electrical Engineering, University of Žilina, Slovakia;
4Department of Medical Biology, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Slovakia

tothova@jfmed.uniba.sk

Aims: The number of electromagnetic sources in our environment operating at intermediate frequency is rapidly increasing and so are increasing the concerns about their potential health risks and carcinogenic properties. Intermediate frequency electromagnetic field (IF-EMF) generated by a wireless power transfer system and its impact to biological systems has been poorly investigated and needs to be more elucidated.

Methods: In the present study, SH-SY5Y human neuroblastoma and T98G human glioblastoma cell lines were exposed to 3 mT, 96 kHz electromagnetic field for 30 minutes with the regeneration period of 44 hours. After regeneration, cytotoxic and genotoxic effects of this exposure were assessed by MTT test and comet assay, respectively.

Results: Cell viability for IF-EMF treated and control cells showed no statistical significance in neither SH-SY5Y nor T98G cell line. Moreover, comet assay showed no DNA breaks in these cells after being treated with IF-EMF of 3 mT, 96 kHz for 30 minutes.

Conclusions: In this preliminary study we were unable to detect any negative effect of IF-EMF exposure using biochemical and biological analysis. However, more studies in different exposure conditions are needed to elucidate these findings.

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CONTINUOUS LEVODOPA- CARBIDOPA GEL RECOVERS MOTOR CORTEX PLASTICITY IN ADVANCED PARKINSON'S DISEASE

Kolmancic Kaja[1],*, Prezelj Neza[2], Zupancic K Nina[2], Trost Maja[2], Flisar Dusan[2], Kramberger G Milica[2], Rajnar Robert[2], Pirtosek Zvezdan[2], Kojovic Maja[2]

1Medical faculty, University of Ljubljana, Institute of pathophysiology, Ljubljana, Slovenia;
2University Clinical Centre, Division of neurology, Ljubljana, Slovenia

kaja.kolmancic@gmail.com

Introduction: In Parkinson's disease (PD) chronic pulsatile treatment with oral levodopa causes maladaptive changes in the cortico- basal ganglia- talamo- cortical ciruit, which underlie motor complications such as motor flucuations and levodopa-induced dyskinesias. Using transcranial magnetic stimulation (TMS), these changes may be detected at level of sensorimotor cortex and consist of absent response to plasticity protocols even when patients are tested under dopaminergic medications. Continuous infusion of levodopa- carbidopa gel (LCIG) improves motor complications of PD, but it is unknown if this treatment may reverse maladaptive changes of plasticity.

Methods: Ten patients with advanced PD (average age 72.5, disease duration 14 years) underwent TMS experiments two days before and six months after introduction of LCIG. We measured motor thresholds, input/output curve, intracortical inhibition and response to intermittent theta burst stimulation (iTBS) plasticity protocol over the hemisphere corresponding to more affected side. Patients were in the clinically defined »on« state. Clinical assessment was performed using MDS- UPDRS part III and IV scale.

Results: There was no significant change in the UPDRS part III in the »on« state, however there was a clear trend for improving of motor complications with LCIG (MDS-UPDRS part IV; p=0.1). While response to iTBS was absent on oral dopaminergic medications, LCIG significantly recovered motor cortex plasticity (p=0.020)(Fig.1). There were no changes in other TMS parameters.

Conclusions: LCIG is able to restore impaired response to iTBS, in parallel with improvement of motor complications. Continuous dopaminergic treatment may reverse maladaptive changes related to chronic pulsatile dopaminergic treatment.

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ENDOGENOUS BUT NOT SENSORY DRIVEN NEURONAL ACTIVITY REGULATES ADULT NEUROGENESIS IN THE OLFACTORY BULB

Kaizhen Li*, Xin Su, Yury Kovalchuk, Olga Garaschuk

Department of neurophysiology, Institute of Physiology, University Bern, Bern, Switzerland

li@pyl.unibe.ch

Thousands of adult-born neurons are added to the mouse olfactory bulb on a daily basis. The mechanisms underlying the migration, morphogenesis and survival of adult-born neurons are not clear. In the present work, we studied the roles of endogenous and sensory-driven neuronal activity in the *in vivo* development of adult-born neurons in the mouse olfactory bulb.

We utilized the overexpression of potassium channel, Kv1.2 or Kir2.1, to genetically modify the endogenous activity of adult-born neurons. By using *in vivo* two-photon Ca^{2+} imaging in awake mice, we found that the migration, morphogenesis, odor-evoked responsiveness, and survival rate of were remarkably impaired in Kv1.2- and Kir2.1-overexpressing adult-born neurons after alteration of endogenous activity. Surprisingly, the odor-deprived adult-born neurons displayed normal migration and morphology, thus suggesting that sensory-driven activity did not affect the early development of adult-born neurons. Further analysis revealed that the odor-deprived adult-born neurons maintained a normal level of endogenous activity. Finally, we explored which signaling pathway is involved in the development of adult-born neurons. Our results demonstrated that pCREB expression was down-regulated in Kv1.2- and Kir2.1-overexpressing adult-born neurons. We propose that impaired endogenous neuronal activity inhibits Ca^{2+}-pCREB signaling pathway as well as the expression of pCREB-dependent genes.

In conclusion, our data demonstrate that endogenous but not sensory-driven activity plays a key role in regulating migration, morphogenesis and early-phase survival of adult-born neurons in the mouse olfactory bulb, and identify an important role of Kv1.2/Kir2.1 in the developmental processes mentioned above.

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EXCITATORY RUBRAL CELLS ENCODE THE ACQUISITION OF NOVEL COMPLEX MOTOR TASKS

Giorgio Rizzi, Mustafa Coban, Kelly R. Tan

Biozentrum, University of Basel, 4056 Basel, Switzerland

giorgio.rizzi@unibas.ch

Aim: The Red Nucleus (RN) is required for limb control, specifically fine motor coordination. There is some evidence for a role of the RN in reaching and grasping, mainly from lesion studies, but results so far have been inconsistent. In addition, the role of RN neurons in such learned motor functions at the level of synaptic transmission has been largely neglected.

Methods: WT and Vglut2 mice were tested in several behavioral tasks revealing grosser and finer motor tasks including spontaneous locomotion, elevated grid test and single pellet reaching task. RN cellular characterization was assessed through fluorescent in situ hybridization and *in vitro* patch clamp recording to profile the cells and evaluate plastic excitatory and inhibitory events. Synaptophysin-expressing virus was used to map the RN outputs. Finally, a chemogenetic approach assessed the necessity of RN cells in reaching skills.

Results: We show that Vglut2-expressing RN neurons undergo plastic events and encode the optimization of fine movements. RN light-ablation severely impairs reaching and grasping functions while sparing general locomotion. We identify a neuronal population co-expressing Vglut2, PV and C1QL2, which specifically undergoes training-dependent plasticity. Selective chemo-genetic inhibition of these neurons perturbs reaching and grasping skills.

Conclusions: Our study highlights the role of Vglut2-positive rubral population in complex fine motor tasks, with its related plasticity representing an important starting point for the investigation of mechanistic substrates of fine motor coordination training.

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PREVENTIVE HYPOTHERMIA AS A NEUROPROTECTIVE STRATEGY FOR PACLITAXEL-INDUCED PERIPHERAL NEUROPATHY

Beh Suet Theng[1,2], Lun-De Liao[1] , Yu-Min Kuo[2,3]

1Institute of Biomedical Engineering and Nanomedicine, National Health Research Institutes, Zhunan, Taiwan;
2Institute of Basic Medical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan;
3Department of Cell Biology and Anatomy, College of Medicine, National Cheng Kung University, Tainan, Taiwan

suetthengbeh@gmail.com

Aim:Chemotherapy-inducedperipheralneuropathy(CIPN)isasevereadverseeffectthatoccurssecondarytochemotherapeutic treatments and has no known preventive or therapeutic strategy. Therapeutic hypothermia has been shown to be effective in protecting against central and peripheral nervous system injuries. However, the effects of hypothermia on CIPN have rarely been explored. This study is designed to investigate the neuroprotective effects of hypothermia on the pathophysiology of CIPN.

Methods: CIPN was induced in rats using paclitaxel intravenous infusions, whereas regional hypothermia was induced by placing a temperature-controlled water bag on the surface of the lower back or unilateral hind limb. The neuroprotective effects of hypothermia were assessed in behavioral, electrophysiological, histological, and cytokine tests. Hemodynamics and paclitaxel distribution in peripheral nervous tissues were also evaluated to study the potential effects of hypothermia. Furthermore, tumor-bearing NOD/SCID mice were used to examine whether hypothermia affected the antiproliferative effect of paclitaxel.

Results: Hypothermia alleviates paclitaxel-induced neuropathic pain by inhibited the paclitaxel-induced activation of astroglia and microglia in the spinal cord, macrophage infiltration into and neuronal injury in the dorsal root ganglia and sciatic nerves, as well as the release of pro-inflammatory cytokines in the dorsal root ganglia, sciatic nerves, and spinal dorsal horn. In addition, hypothermia decreased the local blood flow and local tissue concentrations of paclitaxel. Furthermore, we found that regional cooling is achieved with no effect on the contralateral side or the body. Importantly, the antiproliferative effect of paclitaxel was not affected by the distal application of hypothermia.

Conclusion: Early exposure to regional hypothermia is an effective and potential therapeutic strategy for alleviating paclitaxel-induced peripheral neuropathy.

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P152

EFFECTS OF PLAYING TENNIS ON COGNITION: A PILOT STUDY TO EXAMINE HAND PREFERENCE EFFECT

Evrim Gökçe[1], Emel Güneş[1], Serhat Hayme[2], Berk Aşar[3], Evin Aslan[3], Fatmanur Çevik[3], Merve Nur Çetin[3], Osman Asutay[3]

1Ankara University School of Medicine, Department of Physiology;
2Ankara University School of Medicine, Department of Biostatistics;
3Ankara University School of Medicine, Ankara, Turkey

gokcevrim@gmail.com

Aims: This pilot study aimed to explore the effects of playing tennis on cognitive functions and the effects of hand dominance on cognitive performance in tennis players.

Methods: Tennis players and sedentary controls participated in the study (N=23/23). Each group were divided into two groups based on their hand dominance, right-handed and left-handed participants are equally distributed (for each group n=11/12) Hand preference test, exercise background and daily life questionnaires were used for matching handedness, age, education, and sporting levels. The applied cognitive tests based on verbal and visuospatial tasks. Cognitive performance was evaluated with the verbal fluency test, Corsi's block tapping (CBT) test and mental rotation test.

Mental rotation test was performed once bimanually, whereas CBT test was applied separately with right and left hand. Thus we tried to determine the test that better reflects the hand effect.

Results: Left-hand scores on the CBT test were significantly higher in tennis players than the sedentary control group (p=0.02). No significant difference was found based on hand preference in both groups on the cognitive tests.

Conclusion: Tennis is an open skill sport that requires adaptation for continuously changing conditions and goal-directed behaviors. This can improve visuospatial skills and higher scores of tennis players in the left-handed visuospatial task may be associated with this. Besides, the widespread organization of the right hemisphere is an advantage for spatial abilities. Thus, it may create a technical advantage for left-handed tennis players. CBT test could be more indicative than the mental rotation test for visuospatial functions.

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ESTIMATING THE INHIBITORY POSTSYNAPTIC POTENTIALS OF RENSHAW CELLS ON FIRING MOTONEURONS

Mustafa Görkem Özyurt[1], Maria Piotrkiewicz[2], Betilay Topkara[1], Hans Werner-Weisskircher[3], Kemal Sıtkı Türker[1]

1Koç University, School of Medicine, Istanbul, Turkey;
2Nalecz Institute of Biocybernetics and Biomedical Engineering, Polish Academy of Sciences, Warsaw, Poland;
3Dental Practice, Igel, Germany

gozyurt14@ku.edu.tr

Aim: Although Renshaw inhibition (RI) has been extensively studied for decades, its precise role in motor control is yet to be discovered. One of the main handicaps for this is the lack of reliable methods to induce and study RI in conscious human subjects. The aim of this study therefore was to introduce a novel method to study the synaptic profile of the RI in humans.

Methods: We stimulated the lowest electrical threshold motor axons (thickest axons) in the tibial nerve and analyzed the stimulus-correlated changes in discharge of voluntarily recruited low-threshold single motor units (SMUs) from the soleus muscle. A total of 54 distinct SMUs from 12 subjects were investigated using probability and frequency-based analysis.

Results: Stimuli that generated only the direct motor response on surface electromyography induced an inhibitory response in the low-threshold SMUs. The duration of the RI was found to be inversely proportional to the discharge rate of SMUs. Using this important finding, we have developed a method of extrapolation to estimate RI as it develops on a motoneuron in the spinal cord. The frequency methods indicated that the duration of the RI was between 30 to 40 ms depending on the background firing rate of units, and the extrapolation indicated that the RI on silent motoneuron was around 55 ms.

Conclusions: This study establishes a novel methodology for studying RI in human subjects and hence may serve as a tool towards improving our understanding of RI involvement in human motor control.

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PHENYTOIN DOES NOT INHIBIT THE CONTRACTILE RESPONSE OF STRIPS OF PHRENIC NERVE - DIAPHRAGM FROM ABSENCE EPILEPTIC WAG/RIJ RATS TO ELECTRICAL FIELD STIMULATION IN VITRO

Arif Kamil Salihoglu, Ayşegul Kurt, Ahmet Ayar

Karadeniz Technical University, Faculty of Medicine, Department of Physiology, Trabzon, Turkey

aksalihoglu61@gmail.com

Barbiturates and benzodiazepines are effective in controlling seizures but there is a risk of medications with these agents as they may cause respiratory suppression and acute respiratory failure. Possible involvement of diaphragm contractile failure in this effect is not clear. The aim of this study was to investigate possible effects of phenytoin sodium, an antiepileptic related to the barbiturates in chemical structure, on isolated phrenic nerve diaphragm preparation of absence epileptic rats.

Following decapitation, strips of phrenic nerve diaphragm was isolated from WAG/Rij (Wistar Albino Glaxo/Rijswijk) rats and suspended in tissue bath containing physiological saline at 27 0C, continuously bubbled with 95% oxygen+ 5 % CO2. Contractions were induced by electrical field stimulation (EFS) (suprathreshold 10 sec trains of 100 Hz, 200 msec pulse duration, applied by 5 minute intervals). After obtaining basal response, phenytoin was applied to the tissue bath at cumulative manner (1, 3, 30, 100 and 300 uM). Area under the contraction-time curve of contractions were evaluated by response of stimulation train, applied by 5 minute intervals.

Phenytoin did not exert any significant effect on EFS-stimulated contractions at the concentrations tested. Data from this in vitro study indicates that, phenytoin does not inhibit contractility of phrenic nerve diaphragm, although this does not rule out its possible risk of depressive effect on respiratory center.

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POST-ACTIVATION DEPRESSION IN HUMAN NEURONAL NETWORKS RE-EVALUATED

Betilay Topkara[1], Mustafa Görkem Özyurt[1,2], Beatrice Selen Şenocak[3], Abdullah Salih Budan[1], Murat Necdet Yüce[1], Kemal Sıtkı Türker[1]*

1Koç University, School of Medicine, Sariyer, Istanbul, Turkey;
2Koç University, Graduate School of Sciences and Engineering, Sariyer, Istanbul, Turkey;
3Quinnipiac University, Frank H. Netter MD School of Medicine, North Haven, CT, United States

btopkara17@ku.edu.tr

Aim: The monosynaptic reflex evoked using electrical stimulation, the Hoffmann Reflex (H-reflex), in human has been studied extensively. The amplitude variation of this reflex was used as a tool to investigate many neuronal networks in human, including the presynaptic inhibition.We investigated if a type of presynaptic inhibition, post-activation depression (PD) of H-reflex, is modulated with different levels of voluntary contractions, interstimulus intervals (ISIs) and types of isometric contractions in soleus muscle.

Method: Upon stimulation of the tibial nerve in 23 health subjects, peak-to-peak amplitude change of H-reflex was investigated using surface and intramuscular electromyography. Five different levels of voluntary contractions, 17 distinct ISIs vary between 2 ms to 15 s, phasic and tonic muscle contractions were used to investigate the level and nature of PD.

Results: We confirm the previous findings which show weak PD when the voluntary activation is present and/or ISI used to stimulate the nerve is longer than 5 s. Moreover, our data support that PD exerts its full effect immediately with the first conditioning stimulus and this reduction is homogenously distributed to soleus motor pool. The amplitude of H-reflex starting from the second response was almost half of the first at relaxed muscle for ISI of 1 s. As ISI decreased, the level of PD continued to increase until ISI around 15 ms.

Conclusions: We propose a novel hypothesis in which the circuitry responsible for PD involves plateau potentials in interneuronal networks but not neurotransmitter depletion.

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THE EFFECT OF LIGNOSUS RHINOCERUS ON FUNCTIONAL RECOVERY IN THE MOUSE SCIATIC NERVE CRUSH MODEL

Ramazan Üstün[1,2], Elif Kaval Oğuz[2], Gökhan Oto[3], Sıddık Keskin[4], Ayşe Şeker[1] , Filiz Taşpınar[1]

1Department of Physiology, School of Medicine, Van Yüzüncü Yıl University, Van, Turkey;
2Department of Neuroscience, School of Medicine, Van Yüzüncü Yıl University, Van, Turkey;
3Department of Medical Pharmacology, School of Medicine, Van Yüzüncü Yıl University, Van, Turkey;
4Department of Biostatistics, School of Medicine, Van Yüzüncü Yıl University, Van, Turkey

ramazanustun@yyu.edu.tr

Aims: Lignosus rhinocerotis (LR) is one of the most effective medical mushrooms used as remedy to treat a variety of ailments by the Far East indigenous folks. This study aimed to investigate the effect of LR on functional recovery in the mouse peripheral nerve injury model (PNI).

Methods: In the study, five groups will be formed: three experiments, one negative control (sham), one positive control (saline). Sciatic nerve crush was created by exerting a constant force using a non-serrated clamp. Cold water extract (CWE) of LR was administered for eight weeks with three different doses to treat PNI. Post-treatment functional recovery findings were determined by employing by behavioural tests and electromyographic tests.

Results: PNI significantly impaired motor and sensory functions in the saline and the experimental groups when compared to the sham group after crush injury ($p < 0.05$). CWE significantly increased sensory response and motor performance in the compared with the saline group ($p < 0.05$). Besides, CWE significantly improved compound muscle action potential amplitude, motor nerve conduction velocity and latency period ($p < 0.05$).

Conclusion: CWE treatment in injured peripheral nerves resulted in sensory nerve and motor nerve recovery. Lignosus rhinocerotis improves functional recovery in a mouse model of sciatic nerve injury. These data indicate that LR should be further investigated as a potential therapeutic agent for PNI.

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INVESTIGATION OF SYNAPTIC NEUROTRANSMISSION IN THE OREXIGENIC ARCAGRP →PVN NEURAL CIRCUIT BY OPTOGENETIC AND ELECTROPHYSIOLOGICAL METHODS

Yavuz Yavuz[1], İltan Aklan[1], Nilüfer Sayar Atasoy[2], Sami Ağuş[1], Volkan Adem Bilgin[1], Deniz Atasoy[2] and Bayram Yılmaz[1],*

1Yeditepe University, Faculty of Medicine, Department of Physiology, İstanbul, Turkey;
2University of Iowa, Carver College of Medicine, Department of Pharmacology, Iowa City, IA, United States

bayram2353@yahoo.com

Aims: Agouti related peptide (AGRP) expressing neurons in the arcuate nucleus of hypothalamus (ARC), has a central role in regulating appetite and metabolism. It has been shown that activity changes in these neurons are necessary and sufficient to acutely regulate feeding behavior. AGRP neurons send dense intrahypothalamic axonal projections and make synaptic connections to paraventricular nucleus (PVH), which have been shown to be the key downstream target region. Since ARCAGRP →PVN synaptic connection plays a pivotal role in feeding, neuromodulators controlling the strength of this connection are also likely to be critical for appetite regulation. In this study, we aimed to test the pharmacological properties of the ARCAGRP → PVN connection. For this purpose, we investigated effects of norepinephrine, serotonin and other key appetite regulating neuromodulators on the synaptic properties of this connection.

Methods: We used a combination of optogenetic and electrophysiology to study ARCAGRP →PVN synapses. For this we used channel-rhodopsin assisted circuit mapping (CRACM) approach to isolate AGRP axon evoked synaptic currents from PVH neurons and evaluated impact of various neuromodulators.

Results: Our results indicated that application of antagonists for norepinephrine and serotonin receptors work in opposite fashion to potentiate and inhibit ARCAGRP →PVN synapses respectively ($p<0.001$). We also showed that leptin, ghrelin and NPY have limited impact on this connection.

Conclusions: These findings showed that norepinephrine and serotonin receptor antagonists have strong neuromodulator effects on the synaptic connection of ARCAGRP →PVN. Norepinephrine and serotonin act on this neural circuit in the central regulation of food intake.

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THE TOPOGRAPHICAL ORGANISATION OF ENTORHINAL CORTEX LAYER 5A PROJECTIONS

Sau Yee Tsoi, Matthew Nolan, Gülşen Sürmeli

Centre for Discovery Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom

sauyee.tsoi@ed.ac.uk

Aims: To map the cortical targets of entorhinal cortex layer 5a (EC L5a) neurons and examine the layer distribution of its axons; to determine the projection patterns of individual EC L5a neurons.

Methods: Using a combination of viral labelling approaches and transgenic mouse lines, we mapped and quantified brain-wide projections of entorhinal projection neurons.

Results: We have characterized a transgenic mouse line to verify specific genetic access to entorhinal layer 5a neurons. EC L5a axons were detected in every cortical area, although some cortical areas received more projections than others. We have also discovered that within a target area, entorhinal axons had varied layer preferences. Furthermore, we revealed the configurations of projections from single or target-identified subgroups of layer 5a neurons.

Conclusion: EC L5a neurons can be genetically accessed to enable specific labelling and manipulation. The configuration of projections from EC to a diverse set of cortical areas suggests that EC plays the role of broadcasting hippocampal signals to neocortical target structures. Further studies are required to determine how the projections of EC L5a neurons modulate cortical activity to facilitate the formation of memories.

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MELANOPSIN-EXPRESSING RETINAL GANGLION CELLS (MRGCS) INDUCES AROUSAL AND/OR ANXIETY IN MICE

Nina Milosavljevic[1], Jasmina Cehajic-Kapetanovic[2], Christopher A. Procyk[3] and Robert J. Lucas[1]

1Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom;
2Nuffield Laboratory of Ophthalmology, Department of Clinical Neurosciences , Oxford University , Oxford , UK;
3Institute of Ophthalmology, University College London, London, UK

nina.milosavljevic@manchester.ac.uk

Aims: Functional imaging and psychometric assessments indicate that bright light can enhance mood, attention, and cognitive performance in humans. Although indirect evidence links these events to light detection by intrinsically-photosensitive, melanopsin-expressing retinal ganglion cells (mRGCs) there has been no direct proof in any species. Here we set to investigate whether mRGCs have such an immediate effect on mood and behavioural state in mice.

Methods: We used a chemogenetic approach to selectively activate mRGCs, simulating the excitatory effects of bright light on this cell type in dark-housed mice. We assessed what effect this selective and acute activation of mRGCs has on behavioural state by performing a range of behavioural tests and electrophysiology. We also performed c-Fos (a marker of neuronal activation) mapping of the brain upon mRGCs activation.

Results: Chemogenetic activation of mRGCs evoked circadian phase resetting and pupil constriction (known consequences of mRGC activation). mRGC activation excited numerous thalamic, hypothalamic, and limbic brain regions. In standard behavioural tests (open field and elevated plus maze), mRGC activation induced behaviours commonly interpreted as anxiety-like or of increased alertness. Similar changes in behaviour could be induced by bright light in wild-type and rodless and coneless mice, but not melanopsin knockout mice.

Conclusions: We show that acute activation of mRGCs induces signatures of arousal and/or anxiety in mice. This response is retained in rodless and coneless mice and lost in melanopsin knockouts, confirming that an increase in alertness is a natural light response for which mRGCs are both necessary and sufficient.

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PHYSIOLOGICAL AND MORPHOLOGICAL CHARACTERIZATION OF IDENTIFIED DOPAMINERGIC NEURONS IN THE MOUSE MIDBRAIN AND OLFACTORY BULB

Maggy Yu Hei Lau, AutLau YH, Jones S, Galliano E

Dept. Physiology, Development and Neuroscience, University of Cambridge, Cambridge, United Kingdom

yhl52@cam.ac.uk

Heterogeneity exists between brain dopaminergic (DA) neurons in physiology, connectivity, morphology and gene expression. For example, midbrain DA neurons (Substantia Nigra pars compacta, SNc and the Ventral Tegmental Area, VTA) exhibit different neurotransmitter co-release and projection targets (Morales and Margolis, 2017); while olfactory bulb (OB) DA neurons exist in two subclasses, categorized by the presence of an axon initial segment (AIS) (Galliano et al., 2018). Given the heterogeneity of DA neurons, how do we characterize their physiology, and can we attribute the observed physiological heterogeneity to neuronal subclasses?

We performed whole-cell patch clamp recording in acute slices of midbrain and OB taken from juvenile DAT-TdTomato transgenic mice (P15-37). Under identical conditions, current clamp experiments were performed to examine single-spike properties (spiking threshold, amplitude, width and afterhyperpolarization) and continuous firing properties (input-output spiking frequency, interspike intervals and first action potential delay). Our data show that the input-output firing frequencies were similar between SN, VTA and putative AIS-negative OB DA neurons; while putative AIS-positive OB DA neurons fired at a higher frequency. We next examined the effects of tonic neurotransmitter signalling on physiological properties of DA neurons by the application of picrotoxin (100uM) and DNQX (10uM). In the presence of synaptic blockers, input-output firing frequencies decreased in SN, VTA and putative AIS-positive OB DA neurons; while firing frequency of putative AIS-negative OB DA neurons substantially increased.

Our data further highlight striking functional heterogeneity within and between DA neuron subclasses.

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QUANTIFICATION OF FUNCTIONAL NETWORK ELECTROPHYSIOLOGY FROM STEM CELL DERIVED NEURONS IN MULTIWELL MICROELECTRODE ARRAY TECHNOLOGY

Konstantinos Gkatzis, Heather B Hayes, Anthony M Nicolini, Colin A Arrowood, Daniel C Millard

Axion BioSystems, Atlanta, GA, United States

kgkatzis@axionbiointl.com

Aims: Owed to the rapid advances in stem cell technology, iPSCs are becoming widely adopted in vitro model for studying the development of neural diseases and for screening applications in drug discovery and safety. In order to effectively characterise these models and extract predictive information, measurements of electrophysiological activity across a networked population of neurons provides a comprehensive view of function. Microelectrode array (MEA) technology, in which a planar grid of microelectrodes interfaces with cultured neuronal networks, is optimally suited for characterising the network electrical activity in iPSC-derived neuronal preparations.

Methods: iPSC-derived neuronal cultures were evaluated on the Maestro Pro multiwell MEA platform. The cells were cultured on 48-well MEA plates and monitored throughout maturation of the network connections. Advanced metrics describing the activity, synchrony and oscillations of the functional population activity were computed in response to ion channels blockers and compounds altering synaptic activity.

Results: Maturation of the cultures during time was confirmed through the evolution of electrophysiological metrics linked to network activity (mean firing rate, bursting and synchronous network burst). These metrics allow accurate representation of the effect of known ion channel blockers on the network excitability and of changes in network function by genetic manipulation of the cells in models of central nervous system diseases.

Conclusion: These results support the continued development and use of iPSC-derived neuronal network assays on multiwell MEA technology for high-throughput evaluation of phenotypic disease-in-a-dish models of neural disease, drug discovery, toxicological and safety screening, stem cells characterisation and optimisation.

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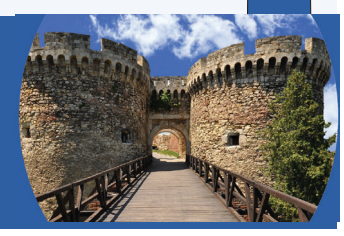

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P163

THE PREBIOTIC LACTULOSE DOES NOT AFFECT OLFACTORY NEUROGENESIS IN A SHEEP MODEL OF EARLY LIFE STRESS

Roberta Vitiello[1,2,3], Maryse Meurisse[1], Frédéric Lévy[1], Céline Parias[1], Scott Love[1], Muriel Darnaudéry[4], Cathy Dwyer[2], Elodie Chaillou[1], Raymond Nowak[1]

1 UMR PRC, INRA, CNRS, IFCE, Université de Tours, Nouzilly, France. 2Scotland's Rural University College (SRUC), Easter Bush, Midlothian, Scotland. 3R(D)SVS, University of Edinburgh, Easter Bush, Midlothian, Scotland. 4Univ. Bordeaux, INRA, Bordeaux INP, NutriNeuro, UMR 1286, Bordeaux, France.

roberta.vitiello@inra.fr

Aims: The olfactory bulb and the hippocampus represent the main regions in the mammalian brain where new neurons continue to be added throughout life. There is a growing body of evidence showing that modifications in gut microbiota affect the host's postnatal hippocampal neurogenesis, especially under stress conditions. However, data regarding the impact of gut microbiota changes on olfactory neurogenesis are lacking. Here, we investigate the effect of the prebiotic lactulose – a non-digestible disaccharide promoting the growth of beneficial gut bacteria – on bulbar neurogenesis in maternally deprived lambs, a sheep model of early-life stress.

Methods: Twenty-four female lambs were separated from their mothers 24 hours after parturition and randomly assigned to the Prebiotic group (P, N=12) or the Control group (C, N=12), housed separately. P lambs were fed with lactulose-supplemented (1%) artificial milk, while C lambs with non-supplemented artificial milk. At eleven weeks of age, olfactory neurogenesis was investigated by quantifying the number of neuroblasts (visualized with doublecortin (DCX) immunostaining) in the granular layer of the main olfactory bulb (MOB). DCX-positive cells were counted manually in frontal sections of the left MOB (four per animal) using Mercator software.

Results: The number of DCX-positive cells observed in the granular layer of the left MOB did not significantly differ (P=0.284) between P lambs (median=33.75 cells/mm2) and C lambs (median=29.50 cells/mm2).

Conclusions: We found no evidence that lactulose supplementation affects olfactory neurogenesis in maternally deprived lambs. However, it remains to be determined whether lactulose can modulate hippocampal neurogenesis in animals exposed to early-life stress.

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OPTOGENETIC MANIPULATION OF CYCLIC NUCLEOTIDES IN HIPPOCAMPAL NEURONS

Oana M. Constantin[1], Shiqiang Gao[2], Shang Yang[2], Georg Nagel[2], Thomas G. Oertner[1], Christine E. Gee[1]
[1]Institute for Synaptic Physiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[2]Biocenter, University of Würzburg, Würzburg, Germany

oana.constantin@zmnh.uni-hamburg.de

Aims: The cyclic nucleotide cAMP is ubiquitously expressed in eukaryotic cells. In neurons, cAMP has been implicated as a key second messenger mediating activity-dependent synaptic plasticity. Most studies used forskolin stimulation of endogenous adenylyl cyclases combined with inhibition of phosphodiesterases to induce synaptic potentiation. While effective at inducing synaptic potentiation, such tools affect all cell types in the preparation. We are thus interested in developing light-activated adenylyl cyclases (soluble and membrane-bound) that produce cAMP only in transfected cells.

Methods: We report the development of highly effective, blue- and green-light-activated, soluble and membrane-bound adenylyl cyclases with strong specificity for cAMP. Spectral sensitivities and kinetics were calibrated in pyramidal cells using co-expression of CNG channels and whole-cell patch-clamp of expressing cells. We use these new tools to study the effects of selectively raising cAMP in only the presynaptic or only the postsynaptic compartments of hippocampal Schaffer collateral synapses.

Results: Surprisingly, activation of bPAC (Beggiatoa photoactivated adenylyl cyclase) or newly developed membrane-bound photo-activated cyclase (bPAC-PM) in the postsynaptic CA1 neuron neither affected baseline transmission (EPSCs) nor the threshold for synaptic plasticity. EPSCs recorded in CA1 neurons in response to action potentials evoked in presynaptic CA3 neurons co-expressing bPAC and ChrimsonR were also not affected by raising cAMP with blue light.

Conclusion: These findings suggest that increasing cAMP in either the pre- or the post-synaptic neuron is not sufficient to induce synaptic plasticity, even when combined with synaptic activity. The mechanism of forskolin/rolipram leading to 'chemical LTP' may involve effects on other signaling systems or cell types.

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LONG NON-CODING RNA – TRANSCRIPTION FACTOR REGULATORY NETWORKS IN MAMMALIAN BRAIN DEVELOPMENT

Ninou Elpinickie[1,2], Antoniou Daphne[1], Politis Panagiotis[1]

1Center for Basic Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece.
2Faculty of Biology, School of Science, National and Kapodistrian University of Athens, Athens, Greece

eninou@bioacademy.gr

Aims: With the advent of new generation technologies, a growing list of formerly unknown regulatory RNA species have come into spotlight. Among them, long non-coding RNAs (lncRNAs) have been found to control stem cell pluripotency, carcinogenesis, development and function of several tissues and organs. Although thousands of lncRNAs are expressed in adult mammalian brain in a highly patterned and specific manner, they remain poorly characterized and their roles in brain development have not yet been studied.

Methods: To tackle this question, we initially performed RNA-Seq analysis in the developing nervous system of mouse embryo. Based on this analysis, we identified many lncRNAs highly expressed in neural cells. We focused on lncRNAs, which are transcribed from genomic loci in close proximity with protein coding genes, encoding for critical transcription factors (TFs) in brain development. We hypothesized that these lncRNAs may be implicated in the regulation of neighboring TF genes.

Results: We characterized the changes in the expression profile of the most interesting from the identified lncRNAs-TF pairs during development of mouse brain. In this study, we further investigated the functional role of lncRNA TCONS_00034309 in the differentiation of neural stem cells by in vitro and in vivo overexpression and knock-down studies, using CRISPR-dCas9-KRAB Effector System.

Conclusions: Our data suggest critical roles for this lncRNA in neuronal differentiation and astrogliogenesis during brain development. Our study provides insights into the involvement of lncRNAs in organogenesis and shows how lncRNAs and protein-coding genes form regulatory networks with important functions in neural cells.

P166

CORRELATION OF PAC1 RECEPTOR ISOFORMS (HIP, HOP1) AND MIR137, MIR147 EXPRESSION DURING POSTNATAL DEVELOPMENT IN RAT RETINA

Etelka Pöstyéni, Adrienn Mester, Antónia Stefanov, Viktória Dénes and Róbert Gábriel

Department of Experimental Zoology and Neurobiology, University of Pécs, Pécs, Hungary

etelka91@gamma.ttk.pte.hu

Pituitary adenylate cyclase-activating polypeptide belongs to the vasoactive intestinal peptide/secretin/ glucagon peptide family members and has been studied extensively because of its diverse biological function. During the development process, its effects are mediated by three types of receptors: PAC1R, VPAC1 and VPAC2, with PAC1 possessing six different isoforms (Null, Hip, Hop1, Hop2, Hiphop1, Hiphop2) as a result of RNA splicing. Our previous results show that out of this six isoforms, four (Null, Hip, Hop1, Hiphop1) are expressed in the rat retina during P5-P20 and from these Hip and Hop1 isoforms are present at the highest level.

Our aim was to test for correlations between the expression patterns of two PAC1 receptor isoforms (Hip, Hop1) and the expression profiles of two microRNA populations (mir137, mir147) which are sequence-specific for Hop1 and Hip isoform mRNAs sequences.

In our experiments, we used Wistar rats aged P5-P10. After RNA isolation from the retina, expression levels were measured through quantitave polymerase chain reaction and a statistical analysis of our results was performed.

We found significant ($p<0.05$) difference and correlation between the expression levels of Hip/Hop isoform types and mir137/ mir147 expression.

Through a better understanding of the complex process of PAC1R isoform switching, these findings provide further insight into the regulatory mechanisms that govern retinal development.

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POSTER SESSION 2

P167

RETINAL GLUTAMATE TRANSPORTERS (VGLUT1, EAAT5) IN ROD BIPOLAR CELLS OF FOUR MAMMALIAN SPECIES

Adrienn Mester[1], Etelka Pöstyéni[1], Róbert Gábriel[1,2]

[1]Department of Experimental Zoology and Neurobiology, University of Pécs, Pécs, Hungary. [2]János Szentágothai Research Centre, University of Pécs, Pécs, Hungary

mesteradri@gmail.com; gabriel@gamma.ttk.pte.hu; gabriel@ttk.pte.hu

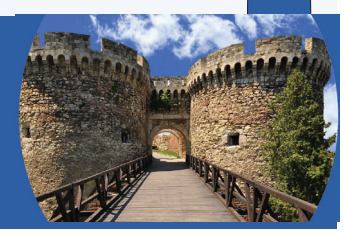
It has long been known that bipolar neurons release the excitatory transmitter glutamate, the major excitatory neurotransmitter in the central nervous system. Bipolar neurons use glutamate and express glutamate transporters such as the vesicular transporter VGLUT1 (which can pack the neurotransmitter into synaptic vesicles) and excitatory amino acid transporters (EAAT5).

In this study the retinal rod bipolar cells with axon terminals in the inner plexiform layer were examined, the presence of glutamate transporters in sublamina 3 have been studied in four different mammalian species (mouse, rat, degu and sheep).

Using immunocytochemistry, we carried out double-labelling experiments in which protein kinase Cα (PKCα) has been used to visualize rod bipolar cells axon terminals.

Colocalization of PKCα with VGLUT1 and EAAT5 revealed both VGLUT and EAAT5 present in axonal varicosities in sublamina 3. These findings indicate that glutamate is transported into the bipolar cells varicosities and packed into synaptic vesicules in this part of the inner plexiform layer.

Further examinations are under way using triple immunolabeling for PKCα, VGLUT and EAAT5 to prove the presence of glutamate transport in sublamina 3 to provide evidence for the close colocalization of these three markers. Since it is known that glutamate transporters are also expressed in the axon terminals of the rod bipolar cells in sublamina 5 and glutamate is stored in the synaptic vesicles there, it is possible that some release-ready vesicles are already generated in sublamina 3, from which they are further transported to sublamina 5.



P168

PROTECTIVE ROLE OF PACAP IN AGE-RELATED AMYLOID-RELATED DEGENERATIVE PROCESSES

Dora Reglodi[1], Adel Jungling[1], Rémi Longuespée[2], Joerg Kriegsmann[3,4], Rita Casadonte[4], Mark Kriegsmann[2], Tamas Juhasz[5], Sebastian Bardosi[3], Andrea Tamas[1], Balazs Daniel Fulop[1], Krisztina Kovacs[6], Zsuzsanna Nagy[7], Hitoshi Hashimoto[8], Attila Bardosi[3]

1Dept. of Anatomy, MTA-PTE PACAP Research Group. 2Institute of Pathology, University of Heidelberg, Heidelberg, Germany. 3Center for Histology, Cytology and Molecular Diagnostics. 4Proteopath GmbH, Trier, Germany. 5Dept. of Anatomy, Histology and Embryology, Faculty of Medicine, University of Debrecen, Hungary. 6Dept. of Biochemistry and Medical Chemistry. 7Second Dept. of Internal Medicine, University of Pecs Medical School, Pécs, Hungary. 8Laboratory of Molecular Neuropharmacology, Graduate School of Pharmaceutical Sciences, Osaka University, Japan.

dora.reglodi@aok.pte.hu

PACAP is a cytoprotective peptide providing an endogenous control against tissue-damaging stimuli. Dysregulation of neuropeptides may play an important role in aging-induced impairments.

We hypothesized that the progressive decline of PACAP throughout life, the increased vulnerability to various stressors of animals partially or totally lacking PACAP and the well-known general cytoprotective effects of PACAP lead to age-related pathophysiological changes in PACAP deficiency.

Young and aging PACAP knockout mice were used. Detailed histopathological analysis was performed from all organs with Kongo red staining followed by mass spectrometry of the plaques. Serum laboratory tests, cytokine array, PCR and immunohistochemistry were used to analyze details about the amyloid depositions.

Pre-senile appearance of amyloidosis in young PACAP knockout (KO) animals appeared and showed that senile amyloidosis in mice lacking endogenous PACAP was accelerated, more generalized, more severe and affected more individuals. Histopathology showed age-related systemic amyloidosis with mainly kidney, spleen, liver, skin, thyroid, intestinal, tracheal and esophageal involvement. Mass spectrometry–based proteomic analysis, re-confirmed with immunohistochemistry, revealed that apolipoproteinA-IV was the main protein in the amyloid deposits together with several other accompanying proteins. Although the local amyloidogenic protein expression is disturbed in the KO animals, no difference was found in lipid laboratory parameters, suggesting a complex pathway leading to increased age-related degeneration with amyloid deposit in the lack of PACAP.

In summary, here we describe accelerated systemic senile amyloidosis in PACAP knockout mice, indicating an early aging phenomenon. Thus, PACAP KO mice could serve as a model of accelerated aging, with human relevance.

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P169

AGE DEPENDENCY OF C-FOS EXPRESSION IN MALE RAT'S BRAINSTEM STRESS CENTRES AND EXTENDED AMYGDALA

László Ákos Kovács[1,2], Josef Andreas Schiessl[1], Anna Elisabeth Nafz[1], Valér Csernus[1], Balázs Gaszne[1,2]

1Department of Anatomy, University of Pécs, Medical School, Pécs, Hungary. 2Center for Neuroscience, Pécs University, Pécs, Hungary.

laszlo.akos.kovacs@aok.pte.hu

Aims: The key of the stress-response is the hypothalamus-pituitary-adrenal (HPA) axis controlled by the parvocellular paraventricular nucleus of the hypothalamus (pPVN), overregulated by higher-order limbic centres. The HPA axis reactivity is considered to be a function of age, but to date, little is known about the background of this age-dependency. We aimed to assess the stress sensitivity by semi-quantitation of neuronal activity marker (c-Fos).

Methods: We investigated the HPA activity and c-Fos immunoreactivity 2h after the beginning of a single 60min acute restraint stress in eight age groups of male Wistar rats. We hypothesized that the function of the HPA (pPVN c-Fos and blood corticosterone level), the neuronal activity of nine stress-related areas (magnocellular PVN (mPVN), medial (MeA), central (CeA), basolateral nuclei of the amygdala, the oval (ovBNST), dorsolateral (dlBNST), dorsomedial (dmBNST), vent ral and fusiform (fuBNST) divisions of the bed nucleus of the stria terminalis (BNST)), and two brainstem stress centres : the centrally projecting Edinger-Westphal nucleus (cpEW) and dorsal raphe nucleus (DR) may show age-dependent c-Fos response.

Results indicate that the stress-induced rise in blood corticosterone titer was lower in young age reflecting relatively low HPA activity. All 12 stress-related brain areas showed c-Fos response that peaked at 2 months of age. The magnitude of c-Fos immunoreactivity correlated negatively with age in seven regions (MeA, CeA, ovBNST, dlBNST, dmBNST, fuBNST, pPVN).

Conclusions: Stress centres show strong age-dependent both basal and stress induced c-Fos expression, which highlight the importance of further examinations in age and stress associated mood disorders.

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P170

THE ROLE OF DUSP16 IN HIPPOCAMPAL DEVELOPMENT AND ADULT NEUROGENESIS

Sarusi Y[1]., Zega K[1]., Vitic Z[1]., Jovanovic V[1]., Niedzielska M[2]., Lang R[2]., Brodski C[1].

1Zlotowski Center for Neuroscience, Dept. of Physiology and Cell Biology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Be'er Sheva, Israel. 2Institute of Clinical Microbiology, Immunology and Hygiene, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany.

yaelsarusi1@gmail.com

The hippocampus plays an essential role in memory and emotions and is capable to generate new neurons throughout life. Although adult hippocampal neurogenesis has been investigated quite extensively, the embryonic hippocampal development and its transition to adult neurogenesis is less well understood.

Previously we found that mouse mutants lacking a functional Dusp16 gene (Dusp16-/-), which is a dual-specificity phosphatase known to negatively regulate mitogen-activated protein kinases (MAPKs), develop brain overgrowth. We identified a delayed cell cycle exit of neural progenitors in Dusp16-/-mutants as a cause of progenitor overproliferation during mid-gestation. At later gestational stages, this expanded neural progenitor pool generated an increased number of neurons associated with enlarged brain volume.

Unexpectedly, we found that Dusp16-/- showed in contrast to all other investigated brain areas a dramatic reduction in their hippocampus. To study the role of Dusp16 in adult hippocampal neurogenesis, we studied markers associated with this process in the dentate gyrus (DG) of adult heterozygote Dusp16+/- mutants, which are viable and fertile and show no apparent brain malformations. KI67 staining was used as a marker for dividing cells and doublecortin (DCX) as marker for undifferentiated neurons. Interestingly, we found a reduction of KI67+ and DCX+ cells in Dusp16+/- mutant mice, suggesting a reduction in adult hippocampal neurogenesis.

We conclude that Dusp16 plays a specific role in hippocampus formation, which appears to be different to its function in the development of non-hippocampal brain structures. Moreover, our data suggest that Dusp16 is involved in the maintenance of adult hippocampal neurogenesis.

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P171

BMP/SMAD PATHWAY PROMOTES NEUROGENESIS OF MIDBRAIN DOPAMINERGIC NEURONS

Vitic Z[1], Jovanovic VM[1], Salti A[2, 3], Tilleman H[1], Zega K[1], Jukic MM[1], Friedel RH[4], Zou H[4], Edenhofer F[2, 3] and Brodski C[1]

1Department of Physiology and Cell Biology, Zlotowski Center for Neuroscience, Faculty of Health Sciences, Ben-Gurion University of the Negev, Be'er Sheva, Israel. 2Institute of Anatomy and Cell Biology, University Wuerzburg, Wuerzburg, Germany. 3Institute of Molecular Biology, Dpt. Genomics, Stem Cell Biology & Regenerative Medicine, Leopold-Franzens-University Innsbruck (LFUI), Innsbruck, Austria. 4Department of Neuroscience and Neurosurgery, Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

zagavitic@gmail.com

Aims: The embryonic formation of midbrain dopaminergic (mDA) neurons in vivo provides critical guidelines for the in vitro differentiation of mDA neurons from stem cells, currently being developed for Parkinson's disease cell replacement therapy. BMP/SMAD inhibition is routinely used during early steps of stem cell differentiation protocols, including for the generation of mDA neurons. However, the function of the BMP/SMAD pathway for in vivo specification of mammalian mDA neurons is virtually unknown. The overall objective of this study was to investigate the role of BMP/SMAD signaling in the development of mDA neurons in vivo and in vitro.

Methods: Mouse mutants and human induced pluripotent stem cells and induced neural stem cells were used to assess the role of BMPs in mDA formation.

Results: We report here that BMP5/7 deficient mice (Bmp5-/-; Bmp7-/-) lack mDA neurons, caused by reduced neurogenesis in the mDA progenitor domain, but not in the adjacent basal plate. Conditionally inactivating SMAD1 in neural stem cells of mice in vivo (Smad1Nes) hampered the differentiation of progenitor cells into mDA neurons by preventing cell cycle exit. Notably, BMP5/7 robustly increased the in vitro differentiation of human induced pluripotent stem cells and induced neural stem cells to mDA neurons by up to 3-fold.

Conclusions: In conclusion, we have identified BMP/SMAD signaling as a novel critical pathway orchestrating essential steps of mammalian mDA neurogenesis in vivo that balances progenitor proliferation and differentiation. Moreover, we demonstrate the potential of BMPs to improve the generation of stem cell-derived mDA neurons in vitro.

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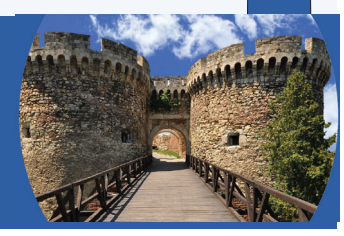

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P172

ELECTRIC AXON GUIDANCE IS MEDIATED BY INTEGRIN: A STUDY USING CONSTANT ELECTRIC FIELD CULTURE AND EMBRYONIC CHICK RETINA

Masayuki Yamashita

Center for Basic Medical Research, International University of Health and Welfare, Japan

my57@iuhw.ac.jp

Aims: Growing axons are directed not only by chemical signals but also by electric fields in a process known as galvanotropism. During retinal development, ganglion cell axons are directed towards the future optic disc by endogenous positive direct current (DC) potentials, which are generated by neuroepithelial cells' sodium transport (Yamashita, BBRC, 2013). However, there is no experimental evidence for the cell surface molecule that is responsible for the electric axon guidance. The present study was aimed at revealing the cell surface molecule involved in the electric axon guidance.

Methods: Retinal strips of chick embryos were cultured in a constant electric field of the same strength as that in vivo (15 mV/mm). They were embedded in Matrigel®, since Matrigel® and the inner limiting membrane, on which ganglion cell axons extend expressing integrin α6β1, contain the extracellular matrix integrin ligands, laminin and collagen. Live axons were stained with calcein-AM. A confocal scanner was used for fluorescence imaging.

Results: Retinal ganglion cell axons extended towards the cathode. Monoclonal anti-chicken integrin β1 antibodies, TASC and W1B10, significantly enhanced the cathodal growth in a dose-dependent manner. Since integrin β1 subunit contains a Ca2+-dependent negative regulatory site and Mn2+ occupies this site to activate integrin, retinal strips were cultured in the presence of Mn2+ and it abolished the electric effect.

Conclusions: These results suggested that binding of the extracellular Ca2+ to the negative regulatory site of integrin β1 subunit regulates integrin activities to direct axons.

Conflict of Interest: None

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P173

SYNAPSE-SPECIFIC, LONG-RANGE HETEROSYNAPTIC METAPLASTICITY IN THE RAT HIPPOCAMPUS

S. Sateesh, O. D. Jones, A. Singh, and W. C. Abraham

Department of Psychology, Brain Health Research Centre, Brain Research New Zealand University of Otago, Dunedin, New Zealand

satsh784@student.otago.ac.nz

Aim: To determine the spatial spread of metaplastic LTP inhibition in hippocampus following priming stimulation in CA1 stratum oriens (SO).

Methods: Field potential recordings were conducted in hippocampal slices of 6-8 week old male Sprague-Dawley rats with area CA3 removed. High frequency "Priming" stimulation was given to CA1 afferents in SO while LTP following theta-burst stimulation was assessed in a second pathway in either SO, stratum radiatum (SR), stratum lacunosum moleculare (SLM) or the middle molecular layer of the dentate gyrus (DG).

Results: It was observed that, 30 min following priming in SO, there was an inhibition of LTP at apical dendritic synapses in SR (Control = 85.5 ± 11.7%; Primed = 20.9 ± 6.3%, p = 0.000129) and at medial-perforant-path synapses of the DG (Control = 55.2 ± 5.5%; Primed = 20.2 ± 7.8%, p = 0.0046). However, LTP was not affected at CA1 apical tuft dendrite synapses in SLM (Control = 56.1 ± 3.6%; Primed = 49.4 ± 7.2%, p = 0.39) or at basilar dendrite synapses in SO (Control = 70.5± 18.9%; Primed = 77.6 ± 16.9%, p = 0.78).

Conclusions: Priming activity generates a long-range metaplastic state that inhibits subsequent LTP elsewhere in the hippocampus in a synapse- and region-specific manner. Hippocampal information processing is thus coordinated in a spatiotemporally selective manner, which may relate to regional differences in LTP mechanisms. The metaplasticity may help to selectively protect recently formed memories from interference, or serve as a neuroprotective mechanism in pathological conditions.

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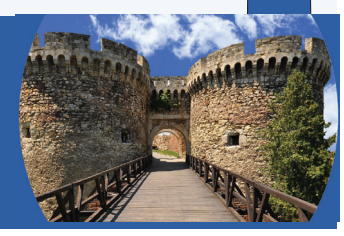

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P174

WHAT DENDRITIC SPINES NEED TO BECOME MATURE? THE ROLE OF SERUM RESPONSE FACTOR (SRF) IN SPINES DEVELOPMENT

Anna Krysiak, Anna Beroun, Leszek Kaczmarek, Katarzyna Kalita

Laboratory of Neurobiology, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland.

a.krysiak@nencki.gov.pl

Aims: Dendritic spines are protrusions on the dendrites where the majority of excitatory neurotransmission occurs. The morphology of dendritic spines change during brain development, and correlate with spine function. Altered spine morphology might underlie the cognitive deficits in neurodevelopmental disorders. Structural plasticity requires expression of many genes, so transcription factors are good candidates for being a regulators of spines maturation process. Serum Response Factor, one of the major transcription factors in the brain, plays a prominent role in various programs of gene expression in the adult brain, but its role in spines maturation is unclear.

Methods: We induced depletion of SRF in neuron from rat primary hippocampal cultures on the early stage of development, before final dendritic spines formation. To do this, we used plasmid or adeno-associated virus with short hairpin RNA to down-regulate SRF in neurons in vitro.

Results: Low level of SRF resulted in an increased number of immature filopodia-like protrusions and decreased number of mushroom spines with the general lack of changes in the overall density of dendritic spines. The analysis of AMPAR-mediated miniature excitatory postsynaptic currents revealed a reduction in the frequency and amplitude of mEPSCs. Western blots analyses showed that SRF-depleted neurons have a lower level of total and surface AMPAR GluR1 and GluR2 receptor subunits.

Conclusions: Depletion of SRF during hippocampal development influences the number of functional synapses and their activity. These findings indicate that SRF regulates transcription of genes essential for spine maturation and synapse formation during development.

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EARLY-LIFE STRESS INFLUENCES MESOCORTICOLIMBIC PATHWAYS OF FEMALE RATS BY ALTERING DENDRITIC SPINE DENSITY IN VENTRAL TEGMENTAL AREA

Anna Gugula, Aleksandra Celary, Grzegorz Tylko, Grzegorz Hess, Anna Blasiak

Institute of Zoology and Biomedical Research, Jagiellonian University, Krakow, Poland

anna.czerw@doctoral.uj.edu.pl

Aims: Childhood trauma causes functional and structural changes in the brain in both humans and animals, leading to increased susceptibility to psychophysiological disorders in adulthood. A crucial role in their development plays changed activity of ventral tegmental area (VTA) originating mesocorticolimbic dopaminergic pathways. Maternal separation (MS), a model of early-life stress, can modify dendritic spine density, and through this mechanism influence neuronal activity. Therefore, current study aimed at determining MS impact on dendritic spine density in VTA, what could serve as a potential neuronal mechanism of mentioned impairments.

Methods: Female rat pups were subjected to MS (removing dam from the home-cage for 3 hours/day from PND 2-14). Control offspring were left undisturbed. Brains of 65 days old rats were stained with Golgi-Cox method. Images of VTA neurons' dendrites were obtained and deconvolved. The location of neurons was described as ventral/dorsal and medial/lateral VTA. Spines were counted on I-III-order branches.

Results: MS caused a significant decrease of dendritic spine density in ventromedial (II-order branches - 15%), dorsolateral (II- and III-order segments - 24-23% respectively) and dorsomedial (I-order branches - 25%) VTA neurons. Ventrolateral VTA neurons were not affected (the decrease reached only 6%).

Conclusions: Observed region-specific changes in VTA dendritic spines density can be connected to a decrease in the number of excitatory synapses and subsequent reduction of dopamine release. This may contribute to alternations of mesocorticolimbic pathways activity and underlie greater susceptibility to addictive behaviors observed in animals and humans subjected to traumatic experiences during development.

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P176

NEURONAL DYSFUNCTION AND BEHAVIOUR ABNORMALITIES IN MICE WITH STARGAZIN MUTATION LINKED TO INTELLECTUAL DISABILITY

Ângela Inácio[1], Gladys Caldeira[1], Susana R Louros[1], Tiago Rondão[1], Nuno Beltrão[1], Marina V Rodrigues[1], Joana Guedes[1], João Peça[1], Ana Luísa Carvalho[1,2]

1CNC-Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal. 2Department of Life Sciences, University of Coimbra, Coimbra, Portugal

ainacio@cnc.uc.pt

Neuropsychiatric disorders, including intellectual disability (ID), are prevalent mental conditions in which cognitive functions such as memory, attention, and executive function are disrupted. Altered neuroplasticity and glutamatergic hypofunction are prominent features of neurodevelopmental disorders, and recent literature points to the involvement of abnormal trafficking of AMPA-type glutamate receptors in the pathophysiology of these diseases. The CACNG2 gene encodes for the synaptic protein stargazin, a member of the Transmembrane AMPA receptor Regulatory Protein (TARP) family of proteins which control the synaptic targeting of AMPA receptors, a mechanism that is crucial for synaptic plasticity. CACNG2 has been singled out as a risk gene for neuropsychiatric disorders and we have found that an ID-associated mutation in this gene results in altered neuronal phenotypes in vitro.

Here, we have evaluated whether stargazin is implicated in the pathogenesis of neurodevelopmental disorders. For that, we designed and characterized a novel knock-in mouse line carrying the ID-linked V143L variant of stargazin.

We found reduced dendritic complexity and decreased frequency of AMPA receptor-mediated mEPSC in CA1 pyramidal neurons, pointing to a disruption in normal information processing. We also found alterations in the structure of post-synaptic densities in the hippocampus. Furthermore, behavioral analysis showed that mice with V143L stargazin mutation manifest impaired object displacement recognition and contextual fear memory, as well as aberrant social interactions.

Our findings demonstrate that mutations in stargazin contribute to neuronal dysfunction and abnormal cognitive behavior, suggesting a role for stargazin in the pathophysiology of cognitive disorders.

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P177

PRENATAL CONTINUOUS LIGHT EXPOSURE LEADS TO CHANGES IN SEROTONIN- AND CIRCADIAN SYSTEM-RELATED GENES EXPRESSION IN THE RAT ADULT OFFSPRING

Chitimus Diana Maria[1], Le Duc Diana[2,3], Voiculescu Suzana Elena[1], Zagrean Leon[1], Torsten Schöneberg[2], Zagrean Ana-Maria[1]

1Division of Physiology and Neuroscience, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania. 2Molecular Biochemistry, Institute of Biochemistry, Medical Faculty, University of Leipzig, Leipzig, Germany. 3Department of Evolutionary Genetics, Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany

chitimus.diana@yahoo.com

Continuous light exposure is a strong stressful stimulus, leading to the disruption of circadian rhythms. Maternal circadian rhythm is involved in the programming of fetal and newborn circadian clocks. Up to date, the impact of prenatal continuous light exposure (PCLE) on adult offspring behavior is still poorly understood.

In order to explore the influence of PCLE on the adult offspring, we investigated the possible substrate of behavioral changes, by assessing melatonin-, serotonin-, oxidative stress-, apoptosis-, and circadian system-related genes expression in different brain areas.

Methods: We exposed pregnant Wistar rats to constant light during late gestation and we measured the melatonin and serotonin levels in the brain homogenates in both the newborn and the adult offspring. qPCR was performed from cDNA of different brain areas to evaluate levels of circadian rhythm-, oxidative stress enzymes-, serotonin-, and circadian-related genes. Among the genes we tested are the melatonin receptors (Mtr1a, Mtr1b), serotonin receptor (Htr1a), serotonin reuptaker (Scl6a4) and circadian genes (Clock, Arntl1, Rora).

Melatonin levels in offspring brains at the time of birth and in adulthood showed a significant decrease both immediately after birth and in adult offspring, while serotonin depletion was significant only in the adult group. Regarding the modified gene expression, the serotonin reuptaker Slc6a4 was down-regulated in the prefrontal cortex of PCLE group, while the circadian rhythm-related gene Rora was up-regulated in the amygdala of PCLE offspring.

Therefore, our results regarding the altered gene expression might indicate a signalling dysregulation, influencing the behaviour of the PCLE offspring.

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POSTER SESSION 2

P178

STEP INHIBITOR, TC-2153 DECREASES AGGRESSION TOWARDS HUMAN IN RATS. THE ASSOCIATION OF AGGRESSION WITH DIFFERENT *BDNF* TRANSCRIPTS LEVELS IN THE BRAIN.

Kulikova E.A., Moskaliuk V.S., Bazovkina D.V., Kozhemyakina R.V., Popova N.K., Kulikov A.V., Naumenko V.S.

Institute of Cytology and Genetics, Novosibirsk, Russia

lisa_kulikova@ngs.ru

Pathological aggression is an important social-economical problem. At the Institute of Cytology and Genetics rats with tame and aggressive behavior towards human were bred. These animals have different levels of brain derived neurotrophic factor (BDNF) protein in the brain. There are eight different transcripts (201-208) of *Bdnf* in rats. BDNF negatively correlates with striatal-enriched tyrosine protein phosphatase (STEP), which is associated with different neuropathology.

The aim of this study was to evaluate the effect of STEP inhibitor (TC-2153) on the behavior and the mRNA level of *Bdnf* transcripts.

Aggressive and tame adult male rats were treated with vehicle, 10 or 20 mg/kg TC-2153. Three hours later the rats were tested in the "glove" and elevated plus-maze (EPM) tests. The mRNA levels of 201-208 transcripts of *Bdnf* were analyzed in hypothalamus, cortex and hippocampus using real-time PCR.

TC-2153 significantly decreased the aggression toward human in the "glove" test and increased the exploration activity in EPM test in aggressive animals in comparison to corresponding vehicle group. In aggressive animals the mRNA level of 206 transcript was significantly higher in all structures, while transcripts 202, 205, 207 and 208 were lower in hippocampus and higher in cortex compared to tame ones.

Thus, STEP inhibitor, TC-2153 decreases aggression. The aggressive and tame rats differ in the level of *Bdnf* transcripts in the brain.

The study was supported by Russian Foundation Grant № 17-15-01021

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P179

PRENATAL HYPERHOMOCYSTEINEMIA DISTURBS DEVELOPMENT OF RAT HIPPOCAMPUS IN EARLY POSTNATAL ONTOGENESIS

Anastasiia D. Shcherbitskaia[1,2], Dmitryi S. Vasilev[1], Natalia L. Tumanova[1], Julia P. Milyutina[2], Irina V. Zaloznyaya[2], Natalia N. Nalivaeva[1], Igor A. Zhuravin[1], Alexander V. Arutjunyan[2]

1I.M. Sechenov Institute of Evolutionary Physiology and Biochemistry Russian Academy of Sciences, St.Petersburg, Russia;
2The Research Institute of Obstetrics, Gynecology and Reproductology named after D.O. Ott, St.Petersburg, Russia

nastusiq@gmail.com

The actions of different stressors during pregnancy lead to various complications both in the maternal organism and in the fetus increasing the risk of abnormal brain development and function in later life. Here we examined the effects of maternal hyperhomocysteinemia (HHC) on development of the brain and hippocampus in rat offspring. HHC was induced in pregnant rats by administration of methionine (0.6mg/kg) in drinking water. In the hippocampus of HHC rat pups during the first week after birth we observed a reduction in the number of pyramidal neurons and increased number of glial cells compared to controls. At the ultrastructural level there were also some features of delayed development: an increased number of growth cones, larger volume of intercellular spaces and decreased number of developed synapses. Alongside with the changes in the cell populations, in the brain of HHC rat pups at this age there was also activation of caspase-3 and increased levels of neuregulin (NRG1), while in the fetal brain in addition to these changes we also observed an increase in proBDNF content. At the same time, despite the increase of IL1-β levels in the HHC mothers' blood, there were no changes in the levels of pro-inflammatory cytokines in the fetal brain. The data obtained indicate that the increased levels of maternal HHC in the embryonic period lead to the disruption of the development of the brain, and in particular the hippocampus, in early postnatal ontogenesis of rats.

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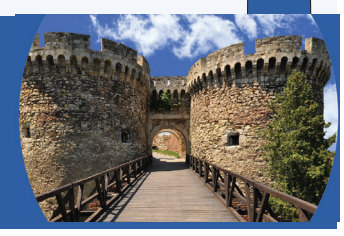

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P180

DNA METHYLATION IS INVOLVED IN MAINTENANCE OF LONG-TERM CONTEXTUAL MEMORY OF HELIX

Alena B. Zuzina, Alia Kh. Vinarskaya, Pavel M. Balaban

Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Saint Petersburg, Russia

lucky-a89@mail.ru

According to recent studies, alterations in chromatin structure and DNA methylation can regulate the cellular and molecular mechanisms underlying fear memory consolidation and reconsolidation processes in snails.

In the present study we investigated whether inhibition of DNA methyltransferase activity affects contextual fear memory maintenance in snails.

We used contextual fear memory model. For training, animals were placed in the training context (on the ball) and shocked for 10 days. For testing, we estimated the percentage of maximal tentacle withdrawal in two contexts: on the ball - context in which animals were shocked ("dangerous" context), and on the flat glass ("safe" context). The DNA methyltransferase inhibitor RG108 was diluted in a sterile saline to the concentration of 2 μM. In all series, 0,1 ml RG108 was injected into the animals.

In the first experiments, we found that that after training the RG108 treatment without the reminder reduced withdrawal amplitude almost to the non-trained values. Testing session next days demonstrated that memory impaired by RG108 injection was reinstated. Since memory reactivation had a rescue effect on contextual memory, we decided to investigate the joint action of DNMTs inhibitor RG108 and the reminder. Application of RG108 1 hour before the reminder didn't affect the withdrawal response amplitudes.

Thus, inhibitor of DNMTs activity impairs the maintenance of contextual fear memory in retrieval-dependent manner – there is no effect when DNMTs inhibition occurs in the presence of memory reactivation. Results support the idea of DNA methylation involvement in maintenance of long-term contextual memory of Helix.

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P182

LONG-TERM EFFECTS OF MATERNAL DEPRIVATION IN RATS ON THE NUMBER OF INTERNEURONS IN THE NEOCORTEX AND HIPPOCAMPUS

Milan Aksic[1], Joko Poleksic[1], Dubravka Aleksic[1], Natasa Petronijevic[2], Nevena Radonjic[3], Gordana Jevtic[2], Maja Jakovcevski[4], Miljana R. Aksic[4], Branislav Filipovic[1], Igor Jakovcevski[5]

1Institute of Anatomy Niko Miljanić, School of Medicine, University of Belgrade, Serbia. 2Institute of Medical and Clinical Biochemistry, School of Medicine, University of Belgrade, Serbia. 3Department of Psychiatry, University of Connecticut School of Medicine, Farmington, CT, USA. 4Department of Anatomy, Faculty of Medical Sciences, University of Kragujevac, Serbia. 5Institute for Molecular and Behavioral Neuroscience, University of Cologne, Cologne, Germany, Center for Molecular Medicine Cologne (CMMC) and German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany.

milanaksic@yahoo.com

Aims: Early life stress has profound effects on the development of the central nervous system. The aim of our study was to examine the effects of early life stress on forebrain circuitry and synaptic activity in the neocortex and hippocampus.

Methods: We exposed 9-day-old rat pups to a 24 h maternal deprivation (MD) and sacrificed them as young adults. We estimated numbers of various immunohistochemically defined interneuron subpopulations in several neocortical regions (prefrontal, retrosplenial and motor cortices) and in the hippocampus. To investigate synaptic activity in the neocortex and hippocampus we analyzed, by immunoblots, the expression of synaptic proteins neuregulin-1 and neurologin-2.

Results: MD rats had reduced numbers of parvalbumin-expressing interneurons in the CA1 region of the hippocampus and in the prefrontal cortex, compared with controls. Numbers of reelin-expressing and calretinin-expressing interneurons were reduced in the CA1 and CA3 hippocampal areas, and unaltered in the neocortex of MD rats. The number of calbinin-expressing interneurons in the neocortex was similar in the MD rats compared with controls. The expression of neuregulin-1 was increased in the neocortex and decreased in the hippocampus of MD rats compared with controls, whereas the opposite was true for neuroligin-2.

Conclusions: Our results indicate complex, cell type-specific and region-specific alterations in the inhibitory circuitry induced by maternal deprivation. Such alterations may underlie symptoms of MD at the behavioral level, and possibly contribute to mechanisms by which early life stress causes neuropsychiatric disorders, such as schizophrenia.

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P183

LONG- AND SHORT – TERM EFFECTS OF ACUTE EARLY LIFE STRESS ON PREFRONTAL CORTEX FUNCTION, SYNAPTIC PLASTICITY AND MICROGLIAL ACTIVATION

Joko Poleksic[1], Milan Aksic[1], Dubravka Aleksic[1], Slobodan Kapor[1], Tihomir Stojkovic[2], Nataša Petronijević[2], Branislav Filipovic[1], Antonios Stamatakis[3]

1Institute of Anatomy "Niko Miljanić", Faculty of Medicine, University of Belgrade, Belgrade, Serbia. 2Institute of Clinical and Medical Biochemistry, Faculty of Medicine, University of Belgrade, Belgrade, Serbia. 3Biology-Biochemistry Lab, Faculty of Nursing, School of Health Sciences, National and Kapodistrian University of Athens, Athens, Greece.

poleksicj@yahoo.com

Aims: Early life adversities can negatively impact brain development and increase susceptability to psychopathologies in later life such as schizophrenia and anxiety. In order to examine the underlying mechanisms we investigated the effects of maternal deprivation on cognitive function, as well as on synaptic plasticity and microglial activation in the prefrontal cortex (PFC).

Methods: On postnatal day 9, whole litters were separated from the dams for 24 hours. Cognitive performace was tested using the behavioral flexibility in a T-maze behavioral task at the age of young adulthood. In the prefrontal cortex, on postnatal days 10 and 60, we measured the levels of brain derived neurotrophic factor (BDNF) and Iba1 using Western blot.

Results: Our results showed that behavioral flexibility was not impaired after the exposure to early life stress. However, the level of BDNF was increased in the deprived group. Furthermore, maternal deprivation did not alter the expression of Iba1 in neonatal or adult PFC. Moreover, a developmental decrease in the levels of Iba1 was detected between neonates and young adults either maternally deprived or not, while no such difference was detected for BDNF.

Conclusions: The results presented herein suggest that acute early life stress such as maternal deprivation may alter synaptic plasticity irrespective of age. Also, the decrease in microglia with age could be explained by the volume expansion of the cortex during brain development.

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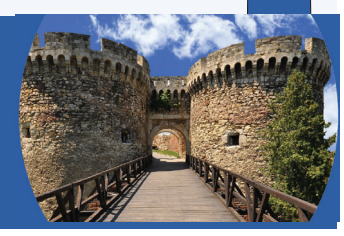

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MORPHOLOGICAL CHARACTERIZATION OF THE HIPPOCAMPUS OF NEONATAL MICE CARRYING THE EPILEPSY MUTATION SCN2A (A263V)

Maja Jakovcevski[1,2], Mohamad Samehni[2], Dirk Isbrandt[2], Igor Jakovcevski[2]

1Department of Anatomy, Faculty of Medical Sciences, University of Kragujevac, Serbia. 2Experimental Neurophysiology, German Center for Neurodegenerative Diseases, Bonn, Germany.

maja@medf.kg.ac.rs; igor.jakovcevski@dzne.de

Aims: A missense mutation in the SCN2A gene (A263V), which encodes the alpha-subunit of the voltage-gated sodium channel Nav1.2, has been linked to associate with childhood epilepsy phenotypes. In this study, we aimed to understand the morphological effects of this gain-of-function mutation on the hippocampus, as a suspected place of onset of the epileptic seizures.

Methods: We studied, by immunohistochemistry, the expression of c-Fos, an immediate early gene, in 7-day-old mice heterozygously carrying the Scn2a mutation (Scn2a mutant mice). Moreover, we investigated presynaptic terminals in the hippocampus of 1-month-old Scn2a mutant mice and analyzed dendritic morphology in Golgi-impregnated sections of these mice, to identify potential morphological changes in the hippocampus caused by this mutation.

Results: We show higher neuronal activation in the hippocampus of 7-day-old mutant mice, as demonstrated by higher c-Fos expression compared to wild-type controls, suggesting hyperexcitability. In 1-month-old mutant mice, dendritic trees of CA1 pyramidal neurons were longer and more branched, and in congruence with this finding, they received more glutamatergic synapses compared to wild-type mice.

Conclusions: Our results support the hypothesis of the hippocampal origin of seizures in Scn2a mutant mice. Furthermore, the hyperexcitable neural circuitry in juvenile Scn2a mutant mice leads to long-lasting changes in dendritic morphology and synaptic inputs.

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P185

SUPER-RESOLUTION MICROSCOPY INVESTIGATION OF THE ROLE OF TENASCIN–C IN SHAPING PERINEURONAL NETS IN THE HIPPOCAMPUS

Ana Jakovljević[1], Michaela Efenberkova[2], Milena Tucić[1], Vera Stamenković[1], Pavle R. Andjus[1]

1Center for laser microscopy, Faculty of Biology, University of Belgrade, Belgrade, Serbia;
2Microscopy Centre - Light Microscopy Core Facility, IMG ASCR, Prague, Czech Republic

ana.jakovljevic@bio.bg.ac.rs

Aims: Perineuronal nets (PNNs) are a specialized form of the condensed extracellular matrix (ECM) primarily involved in the control of central nervous system plasticity. Our aim was to examine how deficiency of the ECM glycoprotein Tenascin-C (TnC) affects the ultrastructural organization of PNNs in the hippocampus by reopening the plasticity window upon rearing animals in enriched environment (EE).

Methods: TnC deficient (TnC-/-) and control wild-type (TnC+/+) mice were reared in EE and standard conditions (SC) for 8 weeks starting from P21. PNNs were fluorescently labeled with Wisteria floribunda lectin (WFA) and imaged using 3D super-resolution Structured Illumination Microscopy. Quantitative analysis of PNN ultrastructure was performed by analyzing different topological parameters and WFA staining intensity.

Results: Even though preliminary data did not reveal pronounced changes in topological parameters, changes in WFA signal intensity were observed. In the CA1 region of the hippocampus, WFA signal intensity was significantly increased in TnC-/- mice reared in EE as compared to the same genotype reared in SC. In addition, the increase in WFA signal intensity was observed in the dentate gyrus of TnC-/- mice compared to TnC+/+ mice, both reared in EE. Interestingly, in the CA2 region, TnC-/- mice reared in SC showed a decrease in WFA signal intensity compared to TnC+/+ mice reared in same conditions. Finally, no significant differences between genotypes or rearing conditions were found in the CA3 region.

Conclusion: Our preliminary data imply region-specific contribution of TnC in shaping the ultrastructure of PNNs in the hippocampus.

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P186

THE EFFECT OF DIFFERENT FAT CONTAINING DIETS DURING GESTATION AND LACTATION PERIODS ON BIOCHEMICAL PARAMETERS, HYPOTHALAMIC AND CEREBELLAR OXIDATIVE STRESS IN OFFSPRING SPRAGUE DAWLEY RATS

Elif Günalan, Cihan Süleyman Erdoğan, Bayram Yılmaz, Burcu Gemici

Yeditepe University, Faculty of Medicine, Department of Physiology, Istanbul, Turkey.

elif_mbg_gunlan@hotmail.com

Aim: The aim of the study was to investigate the effect of exposure of different fat-containing diets during Gestation-Lactation (G-L) periods on hypothalamic and cerebellar oxidative stress and biochemical parameters in Sprague Dawley offspring.

Methods: Mother Sprague Dawley rats were administered with a low-fat diet (LFD), standard fat diet (SFD) and high-fat diet (HFD) during G-L periods. Food and calorie intake were observed daily and mothers were weighted three times in a week. 18 male offspring from three different fat containing groups were obtained after the lactation period (21days). Serum glucose level, plasma insulin and leptin levels, hypothalamic and cerebellar total oxidant status (TOS) and total antioxidant status (TAS) were determined and oxidative stress index (OSI) was calculated. Obtained data were analyzed by One-Way ANOVA and Tukey's multiple comparison tests. $p<0.05$ value was considered statistically significant.

Results: Total calorie intake and body weights of mothers were similar but total food intake was lower in HFD-exposed mother rats ($p<0.05$). Serum glucose and plasma insulin levels were similar in offspring for all groups. However, the plasma leptin level was higher in HFD-exposed offspring ($p<0.05$). While cerebellar TAS, TOS and OSI levels were similar between the groups, hypothalamic TAS decreased in HFD-exposed offspring ($p<0.05$), hypothalamic TOS increased in LFD-exposed offspring ($p<0.05$) and also higher hypothalamic OSI was observed in HFD-exposed offspring when compared to SFD exposed offspring ($p<0.05$)

Conclusion: Maternal-HFD exposure causes increased hypothalamic oxidative stress and plasma leptin levels in male Sprague Dawley offspring's.

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P187

EFFECTS OF PRENATAL STRESS PRIOR TO EARLY LIFE SEIZURES ON PROGENITOR/STEM CELLS, ANGIOGENESIS AND OBJECT RECOGNITION

Çelik Kübra[1], Bilim Petek[1], Garip Gurur[2], Durmaz Burak[3], Yardımcı Ahmet Giray[4], Pamuk Buket Şura[4], Sözmen Eser[3], Baka Meral[2]

1Department of Neuroscience, Institute of Health Sciences, Ege University, İzmir, Turkey. 2Department of Histology and Embryology, Faculty of Medicine, Ege University, İzmir, Turkey. 3Department of Medical Biochemistry, Faculty of Medicine, Ege University, İzmir Turkey. 4Faculty of Medicine, Ege University, İzmir, Turkey.

kubracelik94@gmail.com

Aims: Stress increases the epileptic risk by affecting both embryonic and postnatal development. Therefore we investigated effects of prenatal stress prior to hypoxia and pentylentetrazol (PTZ) exposure on progenitor/stemcells, angiogenesis and synaptic plasticity in hippocampal formation of juvenile rats. We aimed to show the effects of prenatal stress on object recognition, histopathological and biochemical changes on hippocampus of PTZ and hypoxia induced rats.

Methods: The offspring (n=68) of stressed rats by restraining (Embryonic12,5-E17) (n=3) and unstressed rats (n=3) were divided 3 subgroups as PTZ (45mg/kg), hypoxia and control on Postnatal10. day. After the object recognition test was performed on P32, brains were removed on P35 for the immuno/-histochemical and biochemical studies.

Results: After measuring the discrimination index in the object recognition test, it is found that control rats performed the best recognition and the lowest recognition performed by PTZ induced rats. Immonhistochemical studies showed that nestin expression is higher in control groups than prenatal stress while VEGF expression is significantly higher in prenatal stress groups. It was seen that synaptophysin expression differs in CA1 and CA3 especially in prenatally stressed control rats. In biochemical studies, it is found that prenatal stress effected oxidation and antioxidation parameters.

Conclusions: It has been shown that effects of prenatal stress on progenitor/stemcells and angiogenesis of epileptic and hypoxic juvenile rats. As a conclusion this study showed prenatal stress might have a role on histopathological and biochemical changes as well as object recognition in hippocampus of PTZ and hypoxia induced juvenile rats.

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P188

A RISK FACTOR FOR AUTISM: MATERNAL EXPOSURE TO TRIPHENYL PHOSPHITE

Petek Bilim[1], Kübra Çelik[1], Gurur Garip[2], Ahmet Giray Yardımcı[3], Buket Şura Pamuk[3], Meral Baka[1,2]

1Department of Neuroscience, Institute of Health Sciences, Ege University, İzmir, Turkey. 2Department of Histology and Embryology, Faculty of Medicine, Ege University, İzmir, Turkey. 3Faculty of Medicine, Ege University, İzmir, Turkey.

petekbilim@gmail.com; meral.baka@ege.edu.tr

Aims: Autism is one of the neurodevelopmental disorders which is characterized by impairments in social communication and repetitive behaviors. Exposure to environmental chemicals during the embryonic period increase the risk of autism. This study was planned to investigate the effects of maternal intraperitoneal injections (ip) of Triphenyl Phosphite (TPP) which is an enviromental neurotoxic chemical and Valproic Acid (VPA) which is used as an autism model in rats.

Methods: This study has 3 groups: Control, VPA and TPP. There are 3 pregnant rats in each group. Maternal ip was administered 12.5 days of pregnancy. Male offspring (n=10 each group) performed a Three-Chambered Social Interaction Test and Marble Burying Test on P33-P34. Tissues were perfused on P35 for immunohistochemically staining (ihc).

Results: The hippocampal formation was considered. A lower number of Nestin positive cells were detected in the Subgranuler Zone of the control group compared to TPP and VPA group. The results of connexin 43 are also similar to nestin in CA3 region. Synaptophysin expression is less in TPP and VPA group than control. The granular cell layer and CA1 layer are more thinner than TPP and VPA group. Both VPA and TPP group showed similar repetitive behaviors in the Marble Burying test. Results of Three-Chambered Social Interaction Test, both TPP and VPA group showed that the impairments in social interaction.

Conclusions: The results of ihc demonstrated that neuroinflammation and continuation of histogenesis. Behavioral tests indicated that repetitive behaviors and impairments in social interaction. Therefore, exposure of maternal TPP as a risk factor for autism.

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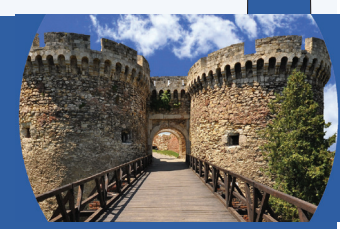

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P189

THE BENEFICIAL EFFECT OF TRANS-RESVERATROL ON EARLY HIPPOCAMPAL NEURODEVELOPMENT IN A RAT MODEL OF FOETAL ALCOHOL SYNDROME AND HYPOXIC-ISCHEMIC ENCEPHALOPATHY

Maria-Miruna Costreie, Nikolaos Zygouropoulos, Mara Iesanu, Artsiom Klimko, Sebastian Isac, Leon Zagrean, Ana-Maria Zagrean

Physiology and Neuroscience, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

mar_miru@yahoo.com

Aims: Neonatal Hypoxic-Ischaemic Encephalopathy is a devastating pathological condition which imposes a significant social and economic burden worldwide. Maternal ethanol consumption causes deleterious effects on the prenatal brain development which may increase its vulnerability to hypoxia/ischemia. A potential therapeutic agent could be trans-resveratrol, a dietary polyphenol with antioxidant and antiapoptotic properties. The aim of the current work was to assess the role and impact of maternal diet in modulating the severity of HIE, secondary to perinatal asphyxia (PA) by: 1) introducing ethanol as a teratogen (hypothesised to exacerbate hippocampal damage induced by PA in the neonatal brain) and 2) by introducing trans-resveratrol (hypothesised to have restorative effect and attenuate the damage).

Methods: Neuroinflammation, neural injury and epigenetic changes of the immature hippocampus, were assessed by measuring levels of tumour necrosis factor alpha (TNF-alpha), S100-beta protein and methyl CpG binding protein 2 (MeCP2) in hippocampus homogenate obtained from P7 Wistar rats, via ELISA.

Results: The present results suggest that ethanol and PA have a cumulative effect in increasing levels of S100-beta and TNF-alpha ($p < 0.0001$) and slightly decreasing levels of MeCP2, while trans-resveratrol rescues levels of MeCP2.

Conclusion: Here, it is suggested that ethanol can exacerbate neuronal damage in neonates further exposed to PA, even if consumed briefly during pregnancy, while trans-resveratrol has the potential of rescuing some of this damage. This promising approach should be further investigated in experimental and clinical models, as deepening of our knowledge about maternal diet and prevention of perinatal insults could improve lives dramatically.

P192

CHARACTERIZATION OF NOVEL PYRAZOLOQUINOLINONES WITH LOW AFFINITY FOR BENZODIAZEPINE BINDING SITES

Fabjan. J.[1], Iorio, M.T.[2], Bampali, K.[1], Siebert, D.C.B.[2], Steudle, F.[1], Scholze, P.[1], Mihovilovic, M.D.[2], Ernst, M.[1]

1Center for Brain Research, Medical University of Vienna, Vienna, Austria. 2Institute of Applied Synthetic Chemistry, Technical University of Vienna, Vienna, Austria.

jure.fabjan@meduniwien.ac.at

Ligands selective for extracellular alpha+/beta- binding sites of GABAA receptors, with low binding affinity for benzodiazepine binding sites are of great interest.

In the present study we aimed to explore the effect of position R6 of ring A of pyrazoloquinolinones on their selectivity for the homologous extracellular alpha+/beta- and alpha+/gamma- binding sites.

To this end, we synthesized and characterized six pyrazoloquinolinones with specific substitutions on the position of interest and subsequently characterized their pharmacological profiles. Benzodiazepine binding site affinity was assessed with [3H]-flunitrazepam displacement assays, while the modulatory effect of the ligands on GABAA receptors was tested with two electrode voltage-clamp electrophysiology in Xenopus laevis oocytes.

The displacement assay results show a low binding affinity to benzodiazepine binding sites for two ligands with hydrophobic R6 residues. These results align with previous observations, where an introduction of a tert-butyl residue on the same position abolished the affinity for benzodiazepine binding sites. These compounds also exhibit strong positive modulation in alpha1beta3 GABAA receptors, which we attribute to interaction of the ligands with the extracellular alpha+/beta- interface.

Our results provide a confirmation of previous observation that position R6 of ring A in pyrazoloquinolinones affects binding to benzodiazepine binding sites, while leaving room to still retain modulatory effects with useful potency, originating from interaction of the ligands with alternative sites.

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P193

A NOVEL GABAA-RECEPTOR ALPHA5-SUBUNIT-SELECTIVE BENZODIAZEPINE, WHICH PRIMARILY INTERACTS WITH LOOP C OF THE SUBUNIT

Petra Scholze, Xenia Simeone, Filip Koniu, Markus Müllegger, Andreas Smetka, Friederike Steudle, Roshan Puthenkalam, Margot Ernst

Center for Brain Research, Medical University of Vienna, Austria

petra.scholze@meduniwien.ac.at

The family of GABAA receptors is an important drug target in the treatment of sleep disorders, anxiety, epileptic seizures and many others. The most frequent GABAA-receptor subtype is composed of two alpha two beta and one gamma2-subunit, while the nature of the alpha-subunit critically determines the properties of the benzodiazepine binding site of those receptors. Nearly all of the clinically relevant drugs target all GABAA receptor subtypes equally. In the past years, however, drug development research has focused on closer studying alpha5-containing GABAA receptors. Although those receptors are rare (<5% of total) and their distribution is limited to few brain areas like hippocampus, they are believed to be promising future drug targets to potentially treat cognitive and/or mood disorders.

Here we investigated a novel compound derived from the previously described imidazobenzodiazepine SH-053-2 –F-R-CH3, which is moderately selective for alpha5-subunit containing GABAA receptors.

Using two-electrode voltage clamp electrophysiology in Xenopus laevis oocytes and radioligand displacement assays with HEK 293 cells, we demonstrated that an acid group as substituent on the imidazobenzodiazepine scaffold leads to large improvements of functional and binding selectivity for alpha5beta3gamma2 over other alphaxbeta3gamma2 GABAA receptors.

Atom level structural studies provide a hypothesis for the improved affinity to this receptor subtype, which was confirmed by mutational analysis. With this novel alpha5-subunit-selective drug we propose to have discovered a future promsising drug candidate.

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POSTER SESSION 2

P194

STRUCTURE GUIDED GABA-A RECEPTOR LIGAND DEVELOPMENT: A SHOWCASE, CHALLENGES AND PERSPECTIVES

Iorio, M.T. [2], Bampali, K. [1], Simeone, X. [1], Scholze, P. [1], Mihovilovic, M.D. [1], Ernst, M.[1]

1Center for Brain Research, Medical University of Vienna, Vienna, Austria. 2Institute of Applied Synthetic Chemistry, Technical University of Vienna, Vienna, Austria

margot.ernst@meduniwien.ac.at

The aim of this study is to understand cross reactivity between seemingly dissimilar allosteric sites of GABA-A receptors. Many allosteric binding sites exist in heteropentameric GABA-A receptors, among them sites for benzodiazepines, pyrazoloquinolinones, etomidate and barbiturates. Diazepam not only binds at the high affinity extracellular “canonical” site, but also at sites in the transmembrane domain (TMD) that were thought to be shared with e.g. etomidate. Many ligands of the benzodiazepine binding site interact also with multiple additional sites in the extracellular domain and in the TMD, among them the pyrazoloquinolinones that exert strong allosteric modulation.

Recent structural data provides us with 3D coordinates of both classes (extracellular and transmembrane) of diazepam binding sites, which allows the development of structure based pharmacophore models.

Methods: Medicinal chemistry approaches including structure based pharmacophore modelling and functional studies in recombinant receptors are used to develop novel GABA-A receptor targeting scaffolds. The result of a pharmacophore based approach based on pyrazoloquinolinones resulted in novel scaffolds of GABA-A receptor positive modulators. These compounds display promising activity as modulators, but seem to act at a site different from the targeted one. The recent structural provides evidence for a core set of pharmacophore features common to extracellular “benzodiazepine” sites with “etomidate” binding sites in the transmembrane domain. To conclude, we discuss here the similarities and differences of the allosteric sites of interest and a path forward for improved selective targeting.

P195

PHAGOCYTIC ACTIVITY OF CORTICAL ASTROCYTES VERSUS THAT OF MICROGLIA AT LIPOPOLYSACHARIDE-INDUCED INFLAMMATION

Gunel Ayyubova, Shahla Huseynova, Leyla Yildirim, Shahana Gurbanova, Sabina Israfilova

Department of Cytology, Histology and Embryology, Azerbaijan Medical University, Baku, Azerbaijan

gunel.ayubova@gmail.com

Aims: It is well known that peripheral lipopolysaccharide (LPS) activates brain neuroglial cells and ultimately leads to chronic neurodegenerative disorders. Despite of that microscopic abnormalities caused by LPS are subtle and detailed descriptions of the brain cells in inflammatory conditions are required for accurate explanation of their morphologic neuropathology. In a mouse model of neuroinflammation we investigated the phagocytic activity of brain glial cells.

Methods: Adult male white rats were treated intravenously with either LPS (1.0 mg/kg) or 0.9% sterile saline alone. Randomly selected sections of brain cortex were examined by means of light and electron microscopy.

Results: In cortical microcirculatory vessels of experimental animals the disturbances in the integrity of blood-brain barrier were found. Nevertheless the conspicuous feature of brain parenchyma was detection the degenerating neurons. Swollen perivascular astrocytic endfeet with phagocytosed material containing fragments of nerve cells, myelinated nerve fibers etc. were observed around cortical capillaries. The cells that showed morphology of activated microglia in close vicinity and immediate contact with shrunken neurons were as well identified. However, the phagolysosomes were evident in only a few of cortical microglial cells.

Conclusion: According to results of research we suggest that phagocytic activity of cortical astrocytes is more intense and profound than that of local microglia in early stages of neuroinflammation. Further examination of molecular mechanisms underlying the ultrastructural degeneration caused by administration of low doses of LPS will likely create a new avenue for the development of novel prophylactic treatment strategies for complications of brain inflammation.

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P196

PROBLEMS FACING CREATION AND MAINTAINING OF RESTING STATE IN EXCITABLE CELLS

Dimitrov A.G.

Institute of Biophysics and Biomedical Engineering – Bulgarian Academy of Sciences, Sofia, Bulgaria

agd@biomed.bas.bg

Aims: The aim of the study is to identify problems that arise in an attempt to model the resting state of excitable cells.

Methods: Hodgkin-Huxley type computer model with accumulation of Na, K, and Cl ions was constructed. The model included: sodium, delayed rectifier potassium, inward rectifier potassium, and hyperpolarization activated channels together with the sodium – potassium pump of different density. The stability of the obtained equilibrium states was tested by applying external subthreshold current. Contribution of NaKCl-cotransporter and chloride channels was also analyzed.

Results: The pump together with the sodium and potassium channels were able to generate several excitable and one non-excitable equilibrium state. However, the application of a long depolarizing current to the excitable equilibrium states, caused accumulation of extracellular sodium and potassium ions, degradation of potassium gradient and transition of the membrane into the non-excitable equilibrium state. The addition of NaKCl-cotransporter and chloride channels did not improve the stability, as the effects of the chloride channels abolished the effects of the cotransporter.

Conclusions: The presence of a pump is not sufficient for producing and supporting the resting potential. The obtained equilibrium states are not stable enough to represent the resting state of the excitable cells. Possible sources for the additional stability could be other currents in the excitable membrane. Other cell types (like glial ones in the nervous system) could also contribute to the stability of the extracellular environment. Further studies are required to reveal the sources for the stability of the resting state of excitable cells.

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P197

METABOLIC REGULATION OF HIPPOCAMPAL NEURO-PROGENITOR APOPTOSIS AFTER DNA DAMAGE

Yu-Qing Li, Marianne Koritzinsky, C. Shun Wong

Sunnybrook Health Sciences Centre (YQL, CSW), and Department of Radiation Oncology (MK, CSW), University of Toronto, Toronto, Ontario, Canada

shun.wong@sunnybrook.ca

Aims: The tumor suppressor p53 is an important regulator of cell fate after DNA damage. Cell fate response to metabolic stresses has also been recently linked to p53-dependent pathways. Here, we asked if 5'-adenosine monophosphate-activated protein kinase (AMPK), the master sensor of cellular energy balance, might regulate p53-dependent apoptosis of hippocampal neuroprogenitors (NPCs) after irradiation.

Methods: Adult mice with targeted disruption of p53 or prkaa2 (gene that encodes AMPK) in the brain were used to demonstrate the role of p53 and AMPK respectively in radiation-induced apoptosis in hippocampal NPCs. Immunohistochemistry for p53, phospho-p53 (ser-46), AMPK, phospho-AMPK (p-AMPK) and multiple NPC phenotypic markers was used to characterize apoptosis and cell-type specific AMPK and p53 activation after irradiation. Cell numbers were estimated by non-biased stereology.

Results: A radiation dose-dependent increase in p-AMPK but not AMPK immunoreactivity in hippocampus was observed at 8 hours after irradiation. Nuclear p-AMPK staining was localized to neurons, and type-2 and type-3 NPCs. Irradiation induced a robust p53-dependent apoptotic response in type-3 NPCs in subgranular zone of the dentate gyrus. The apoptotic response was associated with increase in immunoreactivity for p53 and phospho-p53 at serine 46. In nestin-Cre:prkaa2fl/fl mice, apoptosis of NPCs in subgranular zone was significantly attenuated compared to nestin-Cre mice and prkaa2fl/fl mice.

Conclusions: AMPK is activated after irradiation, and AMPK deficiency results in attenuation of p53-dependent apoptosis of NPCs in mouse hippocampus. Cellular metabolism may play a role in determining cell fate response such as apoptosis in the central nervous system after DNA damage.

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P198

EXPRESSION OF NEUROPLASTIN IN THE BRAIN CORTEX AND CEREBELLUM OF TOLL-LIKE RECEPTOR 2 KNOCK-OUT MOUSE

Mario Stojanović[1,2], Katarina Ilić[1], Kristina Mlinac Jerković[1,2], Marina Radmilović[1,3], Dinko Mitrečić[1,3], Svjetlana Kalanj Bognar[1,2]

1Croatian Institute for Brain Research, School of Medicine, University of Zagreb, Zagreb, Croatia. 2Department of Medical chemistry and biochemistry, School of Medicine, University of Zagreb, Zagreb, Croatia. 3Department of Histology and embriology, School of Medicine, University of Zagreb, Zagreb, Croatia.

stojanovix.m@gmail.com

The aim of this study was to investigate the expression of two isoforms of synaptic glycoprotein neuroplastin (Np), Np55 and Np65, in the brain cortex and cerebellum of mouse lacking Toll-like receptor 2 (TLR2). Since TLRs are widely expressed in mammalian brain and involved in neurodegeneration and hypoxic stress, TLR2 knock-out (KO) mouse model (B6.129-Tlr2tm1Kir/J) is especially intriguing to analyze Np expression due to following evidence: 1) there is a threefold increase in Np65 in rat forebrain following transient ischemia suggesting a role of Np65 in recovery from ischemic insult; 2) Np contributes to neuronal energy metabolism by acting as chaperone of monocarboxylate transporter MCT2; 3) Np65 KO mice have been found to be more susceptible to ischemic brain lesions. In TLR2 KO mice, attenuated neurodegeneration upon hypoxic stimuli has been described due to reduced microglial activation.

To fill in the gaps in biochemical description of this model we investigated expression of Np55 and Np65 isoforms in brain tissue derived from wt and TLR2 KO mice.

Membrane fractions were isolated from cortical and cerebellar tissue samples dissected from 22 animals, in which expression of two Np isoforms was determined by Western blotting.

Results showed statistically significant increase of both Np55 and Np65 in cortex and decrease of Np55 in cerebellum in male KO vs wt mice.

Obtained data are introduction for a larger study which will address potential interplay of Np and TLR2 as well as influence of hypoxia on Np expression in different brain regions.

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P199

CELLULAR UPTAKE AND PROCESSING OF EXTRACELLULAR TAU AGGREGATES: AN IMPLICATION FOR NEURODEGENERATIVE DISEASES

Narendran Annadurai[1], Marian Hajdúch[1,2], and Viswanath Das[1,2]

1Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacky University, Olomouc, Czech Republic. 2Cancer Research Czech Republic, Olomouc, Czech Republic.

narendran.annadurai01@upol.cz

Background: The endosomal-lysosomal pathway is a critical quality control system in cells that ensures timely clearance of damaged organelles and misfolded proteins. This system tends to decline with age, resulting in an accumulation of misfolded and aggregated proteins that subsequently initiate the aggregation of native proteins, a characteristic hallmark of various neurodegenerative diseases, by largely unknown mechanisms.

Methods: The internalization of tau peptide aggregates (TauAgs), which have an inherent propensity to seed endogenous tau aggregation, was monitored by live-cell imaging in HEK-293 Tau-RD P301S biosensor cells. The endosomal-lysosomal escape of TauAgs and TauAg-induced seeding of native Tau-RD were examined in the presence of inhibitors of endocytic pathways, such as chloroquine, dynasore, and genistein.

Results: Inhibition of endocytosis by dynasore, an inhibitor of GTPase dynamin, reduced the entry of extracellular TauAgs and their colocalization into endosomes in cells. There was no colocalization of TauAgs with lysosomes. Dynasore dose-dependently decreased the aggregation of Tau-RD in biosensor cells by TauAgs.

Conclusion: TauAgs enter cells through dynamin-dependent endocytosis and dynamin inhibition by dynasore results in the reduction of aggregation of Tau-RD in biosensor cells. The absence of TauAgs-lysosome colocalization indicates that TauAgs escape the lysosomal degradation pathway. TauAgs that escape into the cytoplasm nucleates the aggregation of native Tau-RD. Understanding the mechanisms that cause the escape of protein aggregates will provide a foundation for therapeutic approaches targeting protein misfolding pathways in neurodegenerative diseases.

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P200

ALLOSTERIC MODULATION OF P2X2 AND P2X4 RECEPTORS BY TESTOSTERONE DERIVATIVES

Sonja Sivcev[1,2], Barbora Slavikova[3], Marian Rupert[1,4], Milorad Ivetic[1,2], Michaela Nekardova[3,5], Eva Kudova[3], Hana Zemkova[1]

1Institute of Physiology, Czech Academy of Sciences. 2Faculty of Science, Charles University. 3Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences. 4First Faculty of Medicine, Charles University. 5Faculty of Mathematics and Physics, Charles University; Prague, Czech Republic.

sonja.sivcev@fgu.cas.cz

Aims: Purinergic P2X receptors are ATP-gated cation channels which can be modulated by steroids and neurosteroids, but sex steroids such as 17beta-estradiol or progesterone are reported to be inactive. Here, we tested a hypothesis that testosterone, another sex hormone, modulates activity of P2X receptors.

Methods: We designed and synthesized new testosterone derivatives that differed in the structure of ester moiety at position C-17 of the D-ring of the steroid. The effect of testosterone derivatives was examined using electrophysiology and etidium bromide (EtBr) uptake measurement in HEK293T cells expressing recombinant rat P2X2, P2X4 and P2X7 receptors.

Results: Our measurements showed that 1–30 μM 17-beta ester derivatives of testosterone modulate positively the 1 μM ATP-evoked currents in P2X2 and P2X4, but not agonist-evoked current in P2X7 receptor. This effect is reversible, and the comparison of chemical structures and whole-cell recordings revealed that the interactions of testosterone derivatives with P2X receptors depend on the lipophilicity and length of the alkyl chain at position C-17. Testosterone butyrate or valerate increased the sensitivity of P2X2 and P2X4 receptors to ATP, reduced the rate of P2X4 desensitization and similarly as ivermectin, P2X4 receptor-specific allosteric modulator, enhanced the EtBr uptake by HEK293 cells expressing the P2X4 receptor. Testosterone derivatives themselves exhibited no effect on P2X4 receptor deactivation, but antagonized the effect of ivermectin on deactivation in concentration-dependent manner.

Conclusions: These results provide evidence for potentiation of particular subtypes of P2X receptors by testosterone derivatives and suggest a potential role of ivermectin binding site for steroid-induced modulation.

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P201

LECTINS MODULATE THE FUNCTIONAL PROPERTIES OF GLUN1/GLUN3-CONTAINING NMDA RECEPTORS

Marharyta Kolcheva[1,2,3], Katarina Hemelikova[1,2], Kristyna Skrenkova[1,2], Martina Kaniakova[1,2], Martin Horak[1,2]

1Institute of Experimental Medicine of the Czech Academy of Sciences, Prague, Czech Republic. 2Institute of Physiology of the Czech Academy of Sciences, Prague, Czech Republic. 3Department of Physiology, Faculty of Science, Charles University in Prague, Prague, Czech Republic

theridia@gmail.com

Aims: This study examined the roles that N-glycosylation and selected lectins play in regulating the functional properties of GluN1/GluN3 receptors.

Methods: Whole-cell patch-clamp recordings with rapid solution exchange system were performed in transfected HEK293 cells expressing GluN1/GluN3 NMDA receptors. Point mutations were introduced in GluN1 and GluN3 subunits to remove specific N-glycosylation sites.

Results: We found that removing specific N-glycosylation sites alters the functional properties of GluN1/GluN3B receptors. Moreover, we found that the functional properties of both GluN1/GluN3A and GluN1/GluN3B receptors are modulated by a variety of lectins and this effect is likely mediated by a reduction in GluN1 subunit-mediated desensitization. We also found that Aleuria aurantia lectin (AAL) has the most profound effect on GluN1/GluN3 receptors, and this effect is mediated partly by a single N-glycosylation site on the GluN3 subunit (specifically, N565 on GluN3A and N465 on GluN3B). Finally, we found that lectins mediate their effect only when applied to non-activated receptors and have no effect when applied in the continuous presence of glycine.

Conclusions: This study provides evidence to distinguish GluN1/GluN3 receptors from the canonical GluN1/GluN2 receptors and offer explanation how GluN1/GluN3 receptors may be regulated in the mammalian CNS. Also, our study shows that lectins can be used as a potential tool in targeting GluN3-containing NMDARs in vivo for pharmacological purposes.

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P202

PROTEOMIC DATA SUGGEST ALTERED MITOCHONDRIAL FUNCTION, TRAFFICKING AND AUTOPHAGY IN SYNAPTOSOMES OF CYSTATIN B-DEFICIENT MICE

Katarin Gorski[1,2,3], Tuula Nyman[4], Christopher Jackson[5], Veronika Rezov[1,3], Tarja Joensuu[1,3], Brendan Battersby[6], Anna-Elina Lehesjoki[1,3]

1Folkhälsan Research Center, Helsinki, Finland. 2Doctoral Programme in Biomedicine, University of Helsinki, Finland. 3Medicum, University of Helsinki, Finland. 4Institute of Clinical Medicine, University of Oslo and Oslo University Hospital, Oslo, Norway. 5Stem Cells and Metabolism Research Program, University of Helsinki, Finland. 6Institute of Biotechnology, University of Helsinki, Finland.

katarin.gorski@helsinki.fi

EPM1 is a neurodegenerative disorder presenting with myoclonus, epilepsy and ataxia. CSTB mutations underlie EPM1, and the Cstb-/- mouse model recapitulates its key clinical features, myoclonus and ataxia. Our previous data imply alterations in neurogenesis, in synaptic function, and in intracellular transport mechanisms.

Aim: The aim of this study was to investigate the differentially expressed proteome of the cerebellum on synapse-specific and on tissue level in Cstb-/- mice.

Methods: The cerebellar proteome from synaptosomes and tissue homogenates of P14 and P30 Cstb-/- and wild-type mice were analyzed by label free quantitative LC-MS/MS, followed by bioinformatic analyses using softwares STRING, IPA, Cytoscape, and FunRich. Mitochondrial respiration was assessed by High-Resolution Respirometry (O2K, Oroboros instruments).

Results: In cerebellar homogenates, preliminary analysis of the dataset for differentially expressed (DE) proteins (fold change (FC) >50%, $p<0.05$), imply alterations in structural and functional components of intracellular transport systems (protein trafficking; endocytosis signaling), as well as in several mitochondrial and ribosomal protein subunits and pathways. In synaptosomes, the DE proteins (FC >50%, FDR<0.05) cluster into structural and functional members of mitochondria and of protein degradation pathways (ubiquitin-proteasome; autophagy), as well as into proteins involved in synaptogenesis. Ongoing follow-up analyses addressing mitochondrial functionality imply compromised respiration in the cerebellar synaptosomes of Cstb-/- mice.

Conclusion: Proteomic analysis of synaptosomes followed by preliminary functional assaying of mitochondrial respiration suggest impaired mitochondrial function as a pathogenic mechanism associated with CSTB deficiency. These findings, as well as the other identified proteomic alterations, need to be elucidated in further studies.

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P203

REGULATION OF SLEEP AND ENERGY HOMEOSTASIS BY RAPID-ACTING ANTIDEPRESSANTS

Alitalo O[1,2], Kohtala S[1,2], Rosenholm M[1,2], Rozov S[1,2], Rantamäki T[1,2]

1University of Helsinki, Division of Pharmacology and Pharmacotherapy. 2University of Helsinki, SLEEPWELL-consortium, Faculty of Medicine, Helsinki, Finland

okko.alitalo@helsinki.fi

A heterogenic group of different pharmacological and non-pharmacological treatments are able to alleviate the symptoms of depression in just hours after administration. These include ketamine, electroconvulsive shock, and sleep deprivation. However, it is currently unknown how their antidepressant effects are mediated on a neurobiological basis.

Using electroencephalography (EEG), we have demonstrated that as the physiological effects of these treatments subside, a state characterized by sleep-like slow oscillations emerges. Only during this state, the antidepressant-associated biochemical markers become activated, suggesting that they are a result of brain's homeostatic response to an excitatory stimulus rather than a direct pharmacodynamic effect. These markers include the activation of brain derived neurotrophic factor (BDNF) receptor TrkB and the inhibitory phosphorylation of glycogen synthase kinase 3 β (GSK3β), both linked to neuroplasticity.

While the slow oscillation state shares biochemical and electrophysiological properties of deep sleep and sedation by anesthetic drugs, sedation by itself is not sufficient to produce antidepressant effects. Thus, we hypothesize that the antidepressant effects are evoked through the biphasic interplay between excitatory stimulus and the subsequent homeostatic response to it.

In order to better characterize this phenomenon, we have used a variety of translationally valid methods including autoradiographic functional imaging (ARG), EEG, as well as biochemical screening methods such as metabolomics, RNA sequencing, and phosphoproteomics.

Our findings can help us to reach better understanding of intrinsic regenerative mechanisms of brain and develop more efficient and faster acting treatments for depression.

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P204

MECHANISMS OF DISTURBED LIPOPROTEIN METABOLISM IN HUNTINGTON DISEASE

Dan Duc Pham[1,2], Dan Lindholm[1,2]

1Medicum, Department of Biochemistry and Developmental Biology, Medical Faculty, University of Helsinki, Helsinki, Finland; 2Minerva Medical Research Institute, Biomedicum-2 Helsinki, Helsinki, Finland.

dan.pham@helsinki.fi

Aims: Brain is rich in lipoprotein, which is essential for membrane building blocks of neuronal cells and maintenance of lipid homeostasis. The relation of cholesterol to neurodegenerative disease such as Huntington´s diseases (HD) has been shown. However, the precise mechanism of disturbances in cellular cholesterol metabolism is not completely understood. Previous evidence from in vivo experiments has been indicated that mHtt interferes with sterol regulatory element-binding proteins (SREBPs) that may influence factors such as Apo-E and ABCA1.

Methods: HD cells, that include the control (Wild-type) cells expressing 7Q poly repeats of Htt and mutant cells expressing 109Q poly repeats were used. Western Blotting and quantitative PCR were used to analyse the protein and mRNA expression levels.

Results: We observed that the lipoprotein receptor (LDLR) is decreased in the septal neurons expressing mutant 109 polyQ expressing Huntingtin compared with controls.

Conclusions: Downregulation in LDLR may arise because of reduced synthesis or be due to enhanced degradation of the receptor via the action of the E3ligase Mylip/Idol targeting LDLR. We are currently studying these events in mutant Htt expressing cells as well as mouse models for HD.

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P205

EXAGGERATION OF SENSORIAL AND EMOTIONAL COMPONENT DURING POST-OPERATIVE PAIN CHRONIFICATION

Tassou A[1,2], Gilabert D[1], Jouvenel A[1,2], Diouloufet L[1], Mechaly I[1,2], Valmier J[1,2], Capdevila X[2,3], Rivat C[1,2]

1Institute for Neurosciences of Montpellier, INSERM, Institut National de la Santé et de la Recherche Médicale, UMR1051, Hôpital Saint-Eloi, Montpellier, France. 2Université de Montpellier, Montpellier, France. 3Lapeyronie University Hospital and Montpellier School of Medicine, Montpellier, France.

adrien.tassou@inserm.fr

Aims: Chronic pain caused by surgical procedures (CPSP) is a significant clinical problem that seriously impacts postoperative rehabilitation and patient's quality of life. Existing treatments are outdated and ineffective over the long term. For these reasons, CPSP has grown into a health priority and has been included in the new version of the international classification of diseases (ICD-11). The incisional pain model has been extensively used to understand the pathophysiology of acute post-surgical pain but remains poorly relevant for the investigation of CPSP. We have thus characterized pain behaviors and molecular changes in a model of incision-induced pain chronification in mice.

Methods: We performed a double-incision (DI) mouse model of hind paw surgery (2 surgeries performed 7 days apart) in which we evaluated sensory and emotional-related behaviors. Gene and protein expression modifications were also evaluated in the spinal cord (SC). We then compared this model with the classical single incision (SI) model.

Results: Our results show that DI induces exaggerated pain hypersensitivity but also sustained anxio-depressive-related behaviors. Alterations in gene and protein expressions are observed compared to SI, especially an increased Iba1 staining in SC reflecting microgliosis. Strikingly, microgliosis inhibition cures surgery-induced mechanical pain hypersensitivity only in a DI context.

Conclusion: Taken together these results bring the evidence that DI model is closer to what defines CPSP than SI model and suggest a possible role for microglia in post-operative pain chronification. The model would then represent a relevant model to decipher the molecular changes responsible for CPSP.

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P206

IDENTIFYING SENSORY PATHWAYS IN CHARGE OF SETTING THE CIRCALUNAR CLOCK OF CLUNIO MARINUS

Dušica Briševac, Tobias S. Kaiser

Max Planck Research Group Biological Clocks, Max Planck Institute for Evolutionary Biology, Plön, Germany

brisevac@evolbio.mpg.de

Development and reproduction of the marine midge Clunio marinus (Chironomidae, Diptera) are synchronized with the tides by endogenous circadian and circalunar clocks. Previous studies identified moonlight, as well as tidal cycles of temperature and water turbulence as cues (zeitgebers) setting the circalunar clock.

Our goal is to describe sensory pathways in charge of the entrainment and reveal the location of the yet unknown circalunar clock. Clunio laboratory strains were established from animals caught at different locations along the Atlantic coast. These field sites differ in their tidal regimes, which shape the reproduction timing of each population.

We simulated tidal turbulence and moonlight in a laboratory setup, and analysed adult emergence over the lunar month for thirteen laboratory strains.

Recorded lunar rhythms principally reflected the ones observed in the field. However, several strains rendered insensitive to either moonlight or tidal turbulence entrainment. Crossing insensitive and sensitive strains showed that the sensitivity to a distinct zeitgeber is genetically determined. We combined quantitative trait locus mapping and association mapping to identify genes underlying the insensitive phenotype. To further investigate sensory neuronal networks, we are working towards describing the nervous system of Clunio marinus. Moreover, we are optimizing in situ hybridization and immunohistochemistry to study expression patterns of the identified genes. Finally, we are establishing CRISPR/Cas9 gene-editing tool with a goal of knocking out target genes and assessing their role in the clock entrainment.

Downstream of the sensory neurons we may finally uncover cellular components of the circalunar clock.

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P207

AUTOMATED PATCH CLAMP APPLICATIONS FOR INVESTIGATING NOVEL PAIN PATHWAYS

E. Dragicevic, N. Becker, M. Rapedius, T. Goetze, I. Rinke-Weiß, P. Mumm, A. Obergrussberger, S. Stölzle-Feix, C. Haarmann, M. George, A. Brüggemann, N. Fertig

Nanion Technologies, Munich, Germany

elena@nanion.de

Aim: Many ion channels initiate and modulate pain sensations, which requires better and faster methods for testing their roles in pain. Voltage-gated sodium channels (NaV) are attractive targets for investigation of chronic and neuropathic pain. Recently, HCN2 channels emerged as important players in triggering and maintaining signalling in nociceptive neurons.

Methods: We investigated biophysical characteristics and blocker/toxin effects on NaV and HCN channels on larger scale, and performed recordings on cell lines and iPSC-derived neurons, using medium/high throughput automated patch-clamp platforms.

Results: We present voltage and current clamp recordings of classical pain modulation candidates, NaV1.7, NaV1.8 and NaV1.9 channels, and have additionally tackled HCN2 channels. We show current-voltage relationship recorded in NaV1.7 expressing CHO cells, consistent with data obtained using other methods (Vhalf of activation: -24 mV; n=275). We were able to investigate tetracaine state dependence and protoxin II blocking effects. We show that tetracaine exhibited a lower IC50 on the second pulse of the double-step voltage protocol (the inactivated state of the receptor, compared with the resting state). We also show compound affinity and assay stability for the slow inactivated state of hNav1.8 expressed in CHO cells, with Vhalf of activation in good agreement with manual patch-clamp literature. To study these pain channels in a more physiological environment, we used stem cell-derived neurons. In these cells, endogenous NaV-mediated currents were recorded with activation parameters consistent with NaV1.7.

Conclusion: Our results demonstrate that pain pathways can be successfully studied on automated patch-clamp systems, facilitating the discovery of novel pain therapeutics.

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P208

MITOCHONDRIAL RELEASE AND DOWNREGULATION OF MFN2 IN RAT CEREBRAL CORTEX AFTER GLOBAL BRAIN ISCHEMIA

Katarina Klacanova[1], Maria Kovalska[2], Maria Chomova[3], Peter Racay[1,4]

[1]Division Neuroscience of Biomedical Center, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava (JFM CU) Slovakia. [2]Department of Histology and Embryology, (JFM CU) Slovakia. [3]Institute of Medical Chemistry, Biochemistry and Clinical Biochemistry, Faculty of Medicine, Comenius University in Bratislava, Slovakia. [4]Department of Medical Biochemistry, (JFM CU) Slovakia

katarina.klacanova@jfmed.uniba.sk

Aims: The aim of work was to study impact of transient global brain ischemia on the expression of selected proteins involved in mitochondrial dynamics and mitochondria-associated membranes.

Methods: We have focused our interest on Mfn2, DRP1, VDAC1 and GRP75 performing the Western blot analysis of both total cell extracts and mitochondria isolated from either cerebral cortex or hippocampus of experimental animals. Rats were subjected to 15 minutes of global brain ischemia, using four vessel occlusion model, followed by 1, 3, 24 and 72 hours of reperfusion. In addition, analysis of Mfn2 intracellular localisation was performed using laser scanning confocal microscopy.

Results: We have shown that both ischemia and ischemia with reperfusions were associated with significant decrease of Mfn2 in mitochondria isolated from cerebral cortex but not in hippocampal mitochondria. Translocation of Mfn2 to cytoplasm was documented immediately after global brain ischemia in the neurones of cerebral cortex. This translocation was followed by decreased expression of Mfn2 during reperfusion. In addition, significantly elevated levels of VDAC1 were documented in hippocampus homogenates of rats that underwent 15 minutes of ischemia followed by 3 hours of reperfusion and from cortex homogenates of rats that underwent 15 minutes of ischemia followed by 72 hours of reperfusion.

Conclusions: Our results have shown that release of Mfn2 from mitochondria that was observed in early periods of reperfusion might represent an important mechanism of mitochondrial dysfunction associated with neuronal dysfunction or death induced by global brain ischemia.

This work was supported by grants: APVV-16-0033 and VEGA 1/0171/18.

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P209

HIPPOCAMPAL FAST-SPIKING INTERNEURONS SHOW HIGHER FUNCTIONAL VULNERABILITY TO HYPOXIA-ISCHEMIA THAN PYRAMIDAL CELLS

Dimitri Hefter, Paul Grube, Andreas Draguhn, Martin Both

Institute of Physiology and Pathophysiology, Heidelberg University, Heidelberg, Germany

dimitri.hefter@physiologie.uni-heidelberg.de

Aims: Fast-spiking interneurons (FSI) are thought to be more vulnerable to metabolic insults than pyramidal neurons (PYR) due to their high energy demand. As FSI orchestrate synchronous network activity such as gamma and sharp-wave ripple oscillations (SPW-R), impairment of their function following hypoxia-ischemia (HI) implies disturbed network function and excitatory-inhibitory balance, which may lay the basis for development of neuropsychiatric diseases. However, there is an ongoing debate on FSI vulnerability. Here we aim to study the effects of oxygen-glucose deprivation (OGD) on the function of FSI and PYR.

Methods: We employed a model of OGD in acute brain slices exhibiting spontaneous SPW-R and recorded from units in the hippocampal CA3 and CA1 regions using tetrodes. Spikes were sorted with KlustaKwik. Various clustering techniques were tested to optimally differ between FSI and PYR.

Results: Stable unit recordings were feasible in the time course of an OGD experiment. The units could successfully be sorted into putative FSI and PYR using Gaussian mixture models clustering based on the firing distribution (inter-spike intervals, bursting). Putative FSI showed an impaired functional recovery from OGD as compared to PYR (decreased firing frequency and bursting, reduced coupling to SPW-R).

Conclusions: To our knowledge, this study is the first to show increased functional impairment of putative FSI after OGD in direct comparison with pyramidal cells. We can confirm their increased vulnerability; thus, our findings are in support of the hypothesis that a metabolic insult may particularly affect interneurons and lead to an imbalance between excitation and inhibition.

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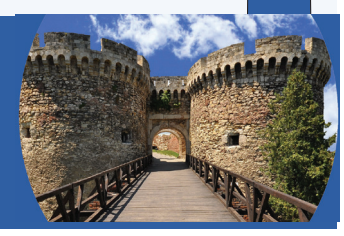

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P210

RELATION BETWEEN NON-CANONICAL CELL MORPHOLOGY AND PERISOMATIC INHIBITION IN HIPPOCAMPAL ENSEMBLE RECRUITMENT

Alexander Hodapp[1]*, Martin E. Kaiser[1], Christian Thome[1], Yevgenij Yanovsky[1], Tina Sackmann[1], Matthias Klumpp[1], Nadja Lehmann[1], Andreas Draguhn[1], Maren Engelhardt[2]*, Martin Both[1]

1Institute of Physiology and Pathophysiology, Heidelberg University, Germany. 2Institute of Neuroanatomy, Medical Faculty Mannheim, CBTM, Heidelberg University, Germany.

a.hodapp@stud.uni-heidelberg.de

The hippocampus exhibits network oscillations called sharp wave-ripple complexes (SPW-Rs) during which neural ensembles are activated, supporting spatial memory formation and consolidation. Canonically, somatodendritic inputs are integrated at the axon initial segment located just next to the soma. Recently, we have shown that in about 50% of CA1 hippocampal pyramidal cells, the axon emerges from a basal dendrite instead. During in vitro SPW-R only these axon-carrying dendrite cells (AcD-cells) generate action potentials (APs). Additionally, these APs initiate abruptly from baseline resembling ectopically generated spikes.

Here we asked, whether the anatomical feature of AcD cells underlies the selective activation of CA1 pyramidal cells during SPW-R.

To test our hypothesis, we performed extra- and intracellular electrophysiological recordings as well as immunofluorescent stainings in acute mouse hippocampal slices while applying picrotoxin, a GABA-A receptor antagonist, exclusively to the recorded cell. This reduction of perisomatic inhibition, recruited nonAcD-cells into SPW-R, and shifted ectopic AP waveforms towards classical APs. To further investigate the correlation of cell morphology to ensemble activity in living animals, we performed preliminary experiments in anesthetized mice. The results suggest a recruitment difference between AcD and nonAcD-cells in vivo.

We hypothesize that AcD-cells are selectively recruited into ensembles during SPW-R, while the firing probability of other neurons is controlled by perisomatic inhibition. Recruitment into SPW-R may not be primarily determined by the strength of inhibition, but by cell morphology. We propose that perisomatic inhibition combined with different axon origins provide a mechanism to rapidly gate and route incoming information.

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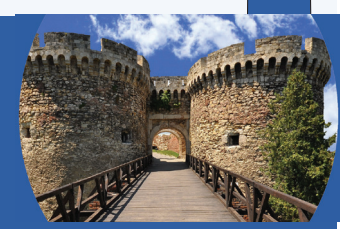

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P211

REDUCED LEVEL OF MICRO RNA IS ASSOCIATED WITH SCHIZOPHRENIA PATIENTS WITH EARLY LIFE STRESS

Lalit Kaurani[2], Rezaul Islam[2], Gaurav Jain[2], Fanny Senner[3,4], Thomas Schneider-Axmann[3], M. Sadman Sakib[2], Tonatiuh Pena[2] , Susanne Burkhardt[2], Nicole Cleve[2], Monika Budde[4], Urs Heilbronner[4], Andrea Schmit[3], Thomas G. Schulze[4], Peter Falkai[3], Farahnaz Sananbenesi[5], Andre Fischer[1, 2]

1Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, Goettingen, Germany. 2Department for Epigenetics and Systems Medicine in Neurodegenerative Diseases, German Center for Neurodegenerative Diseases Goettingen, Goettingen, Germany. 3Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Germany. 4Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Germany. 5Research Group for Genome Dynamics in Brain Diseases, Goettingen, Germany.

lkauran@gwdg.de, andre.fischer@dzne.de

Aim: Schizophrenia (SZ) is a debilitating psychiatric illness. Apart from the genetic predisposition, environment also plays a role as risk factor for developing SZ. Early life stress (ELS) is one of the risk factors associated with developing SZ. The present study sought to unravel differences in the peripheral small RNAome between SZ patients that did or did not experience ELS.

Methods: We analyzed 260 healthy individuals, 82 SZ patients with ELS and 77 SZ patients in this study. The following neuropsychological tests were performed to study cognition: Digit-Span (forward and backward); Digit-Symbol-Test, Trail-Making-Test, and the Multiple-Choice Vocabulary Intelligence Test (MWT-B). Later on small RNA sequencing was performed on these samples. Mouse behaviour and cell culture experiments were performed to validate candidate microRNA expression and their association with Schizophrenia.

Results: We observed cognition impairment in SZ patients compared to controls. Interestingly, cognition was further impaired in SZ patients with ELS. Differential expression analysis revealed a number of microRNAs to be significantly deregulated in patients. Some of these microRNAs were highly expresses in brain and in specific cell types (e.g. Neuron, Astrocyte and Microglia). Manipulation of selected candidate microRNAs in mouse prefrontal cortex region led to Schizophrenia like phenotype in mice.

Conclusion: Via the analysis of blood samples in SZ patients we identify candidate microRNAs that may serve as biomarker and therapeutic targets to treat SZ phenotypes.

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P212

HISTONE METHYLTRANSFERASE SETD1B REGULATES NEURON-SPECIFIC AND LEARNING-RELATED GENE EXPRESSION IN MICE

Cemil Kerimoglu[1], Alexandra Michurina[1], M. Sadman Sakib[1], Julia Cha[1], Dennis Krüger[1], Gaurav Jain[1], M. Rezaul Islam[1], Tonatiuh Pena Centeno[1], Andrea Kranz[2], A. Francis Stewart[2], Andre Fischer[1]*

1German Center for Neurodegenerative Diseases, Epigenetics and Systems Medicine in Neurodegenerative Diseases, University Medical Center Goettingen, Goettingen, Germany. 2Biotechnology Center, Dresden University of Technology, Dresden, Germany.

cemil.kerimoglu@dzne.de; andre.fischer@dzne.de

Aims: In recent years, methylation of histone 3 at lysine 4 (H3K4me) has been shown to be crucial for memory formation and learning-related gene expression in hippocampus. Especially, it has become evident that various closely related H3K4 methyltransferases contribute to memory formation through regulating distinct gene sets and genomic regions.

Methods: We performed a detailed analysis of epigenetic gene expression in CA neurons of Setd1b conditional knockout (cKO) mice by ChIP-Seq and RNA-Seq, and compared the results to those previously obtained by us from two other methyltransferase knockouts – Kmt2a cKO and Kmt2b cKO.

Results: We observe a decrease in H3K4me3 and a concomitant decrease in H3K9ac in Setd1b cKO neurons at learning and plasticity-related gene promoters. We also observe a concomitant downregulation of synaptic plasticity genes. Genes affected by Setd1b knockout are not only different from those affected by the other two methyltransferases, but also are the only ones specifically involved in neuronal functions like synaptic plasticity. This finding is corroborated by our observation that Setd1b-dependent genes have wider H3K4me3 peaks at their promoters than those dependent on Kmt2a or Kmt2b. Moreover, we observe a severe learning impairment in water maze task and an inability to build nests in Setd1b cKO mice.

Conclusions: Our results indicate that Setd1b not only regulates different gene sets from Kmt2a and Kmt2b but also principally differs in its mode of action, uniquely regulating neuron-specific genes. This is corroborated by the evidence that Setd1b regulated genes have wider H3K4me3 distribution at their promoters.

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P213

OPTICAL CONTROL OF CAMKII SIGNALING

Iva Lucic[1], Andrew J. R. Plested[1,2]

[1]Leibniz Institute for Molecular Pharmacology (FMP), Berlin, Germany. [2]Humboldt University, Berlin, Germany.

lucic@fmp-berlin.de

One candidate mechanism for memory formation is long term potentiation (LTP), a form of synaptic plasticity that is characterized by strengthening of synaptic connections between neurons in the brain, lasting from minutes to hours. The first step in LTP is a sharp influx of Ca^{2+} ions, which serves to activate many Ca^{2+}- dependent proteins, one of which is Calcium-calmodulin-dependent protein kinase II (CaMKII). After activation, CaMKII activity apparently becomes Ca^{2+}-independent, and can last for hours after the initial stimulation, implying an important role in LTP. CaMKII forms dodecameric holoenzymes, and one of the proposed features of these holoenzymes is their ability to exchange subunits between activated and unactivated forms and in that way spread kinase activity. However, the structure-function relation for CaMKII remains poorly understood, particularly the structure-activity relation between holoenzymes and the dodecameric form.

Aim: We aim to design and characterize optically-controlled CaMKII mutants in vitro, by endowing CaMKII with unnatural amino acids (UAA) that can serve as covalent crosslinkers upon UV irradiation.

Methods and results: We purified CaMKII endowed with UAA from E.coli, crosslinked them, analyzed their activity and expression in mammalian cells. We identify a mutant that can be crosslinked to calmodulin using UV irradiation in vitro. CaMKII/calmodulin complex is stable and active. We are also able to rescue the same mutant in HEK cells.

Conclusion: The structure-based design of CaMKII mutants shows great promise for the investigation of the relation between CaMKII activation and oligomerization in vitro and in living cells.

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P214

NEUROTRANSMITTER RELEASE INDUCES MEASURABLE THERMAL FLUCTUATIONS IN SYNAPTIC CLEFT

Soltanpour M, Noori HR

Max Planck institute for biological cybernetics, Tuebingen, Germany

morteza.soltanpour@tuebingen.mpg.de

Brain temperature is strongly regulated by cerebral blood flow and shows fluctuations in response to stimuli and neuroactive drugs. Cells in the nervous system not only detect environmental temperature changes through their unique temperature-sensitive molecular machineries but also muster an appropriate response to the temperature change to maintain their inherent functions. However, the mechanisms by which neurons produce, use and transfer heat are largely unknown.

The focus of this study is the latter, namely how temperature gradients are transferred within the synaptic cleft, a process that can affect synaptic transmission by ultimately altering conductivity of post-synaptic ion channels. The dissolution of (charged or polar) neurotransmitters following release from presynaptic terminals within the extracellular fluid has been considered to be driven largely by diffusion. Furthermore, the electric fields of narrow synaptic clefts may also influence synaptic currents. However, how these processes causally relate to heat propagation remains poorly understood, mainly because events inside the cleft are beyond the powers of direct experimental observation.

We use a non-equilibrium thermodynamical model comprised by a system of partial differential equations that describes the changes in intracleft temperature as a function of electrodiffusion of neurotransmitters.

Numerical simulations suggest that transmitter release and propagation correspond to measurable thermal fluctuations ranging from tens to hundreds of mK within the cleft.

The findings provide a plausible description for temperature changes during normal brain activity that are independent from those induced by blood circulation and provide correction-factors for temperature changes associated with diseases such as epilepsy and Parkinson's.

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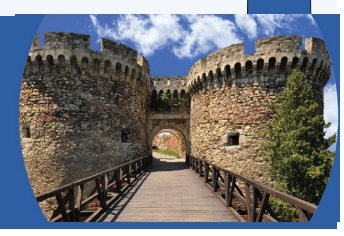

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P215

WHOLE-TRANSCRIPTOME CHANGES IN GENE EXPRESSION IN MULTIPLE TISSUES ACROSS VARIOUS ORGANISMS DURING AGING

Akash Srivastava[1], Emanuel Barth[2,3], Manja Marz[2,3], Otto W. Witte[1]

1Hans-Berger Department of Neurology, University Hospital Jena, Friedrich Schiller University Jena, Jena, Germany. 2Bioinformatics/High Throughput Analysis, Friedrich Schiller University Jena, Jena, Germany. 3FLI Leibniz Institute for Age Research, Jena, Germany.

akash.srivastava@med.uni-jena.de

Aim: The aim of our study was to identify key factors involved in healthy aging and longevity and to gain insight into the evolutionary basis of aging in vertebrates.

Methods: At comparable chronological time-points, we collected tissue samples from organs (blood, brain, liver and skin) of different species (human, mice, killifish and zebrafish) known to be important regulators of physiological aging and performed RNA-Seq followed by data analysis. We have tried to decipher the process of aging on the level of transcriptomics.

Results: We found that the long-lived individuals displayed distinct gene expression patterns and have higher levels of genes associated with protection against ROS and cancer. Aging related processes were also tightly controlled in long-lived individuals. This led to the development of our hypothesis, "individuals who are healthy and live longer manifest expression of protective genes much earlier in life allowing them to live longer.

Conclusions: We tried to dissect and evaluate the data on several parameters and bring forward the results which will help us drive our way towards healthy aging. We found out that every tissue age in a specific manner due to stress induced exhaustion of its primary function. However, there are certain factors like inflammation and mitochondrial dysfunction which universally affect most of the tissues with aging. We could always find certain protection measures among the long-lived individuals and this brings us closer to our initial hypothesis.

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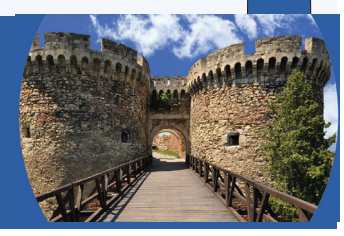

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P216

BRAIN NEUROCHEMICAL CHANGES UNDERLIE DEFICITS IN SOCIAL BEHAVIOUR IN MK-801 -TREATED ZEBRAFISH

Perdikaris Panagiotis, Prouska Pavlina, Saridaki Erasmia-Angeliki, Fokos Stefanos, Dermon Catherine

Laboratory of Human and Animal Physiology, Department of Biology, University of Patras, Greece

perdikarisp@gmail.com

Aims: Social deficits are in the core of clinical symptoms characterizing many neuropsychiatric disorders including Autism Spectrum Disorders (ASD). Zebrafish (Danio rerio), representing highly social animals emerge as a potential model organism to study normal and pathological social phenotypes. The present study aimed to develop a zebrafish model that display deficits in social behavior after sub-chronic MK-801 administration, a non-competitive antagonist of the glutamate N-methyl-D-aspartate (NMDA) and to determine the underlying changes in brain neurochemistry.

Methods: Social deficits were estimated in MK-801 treated zebrafish based on the social interaction (SI) and the Eye Contact (EC) tests, the latter introduced for the first time in zebrafish to quantify the eye contact avoidance behaviour. Possible anxiety levels as well as the presence of specific behavioral stereotypies were determined using the novel tank (NTT) and the open field (OFT) tests. To determine the underlying neurochemical mechanisms, the possible modulation of glutamatergic, GABAergic and noradrenergic neurotransmission was questioned by means of Western Immunoblot analysis of GAD67, mGluR5 and beta2-adrenoceptors expression levels.

Results and conclusions: Analysis of the behavioral parameters showed that MK-801 treated zebrafish exhibited social deficits and increased anxiety levels. In agreement to studies in mammals, an imbalance between brain excitatory and inhibitory neurotransmission was found in zebrafish exhibiting social withdrawal. In addition, protein levels of beta2-adrenoceptors were increased possibly associated to the anxiety-related responses. Taken all together, our results support the importance of this pharmacological zebrafish model to study the neurobiology of social deficits, coupling brain neurochemistry to behavioral phenotypes.

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P217

NR5A2 AFFECTS NEURONAL DIFFERENTIATION OF NSCS IN ADULT HIPPOCAMPUS

M. Tsampoula, I. Antoniadou, D. Gkikas, Y. Koutmani, PK Politis

Center for Basic Research, Biomedical Research Foundation of the Academy of Athens, Greece

ttsampoula@bioacademy.gr

Aims: Neurogenesis in the dentate gyrus (DG) of adult hippocampus is actively involved in brain homeostasis. Identification of novel regulators in adult neurogenesis could significantly contribute to new therapies. To this end, we have recently unraveled the regulatory role of NR5A2, a druggable orphan nuclear receptor, in embryonic neurogenesis. However, its involvement in adult neurogenesis remains elusive. Here, we investigated the involvement of NR5A2 in adult hippocampal neurogenesis.

Methods: Real time RT-qPCR and immunofluorescent analysis were performed to study the expression pattern of NR5A2. Adenoviral-mediated overexpression of NR5A2 in ex vivo cultured aNSCs, and stereotactic injection of Cre-GFP adenovirus to DG of 2 months-old Nr5a2 floxed mice were used to investigate NR5A2 role in adult neurogenesis.

Results: We showed that NR5A2 is expressed in DG of adult hippocampus in much higher levels in neurons than aNSCs or progenitor cells, suggesting a correlation with neuronal differentiation. In agreement, NR5A2 overexpression in ex vivo cultured aNSCs, led to a reduction of proliferation and increase of neuronal differentiation. Moreover, conditional deletion of NR5A2 in DG cells in vivo caused a decrease in the number of NeuN as well as Calbindin positive neurons.

Conclusions: Our data suggest a regulatory role of NR5A2 in adult hippocampal neuronal differentiation and identity. These observations together with the recently discovered pharmacological agonists of NR5A2, render it a candidate target gene for regenerative medicine and aNSC-based treatments of CNS-related diseases and traumas.

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P218

EXPERIMENTAL INFLAMMATORY BOWEL DISEASE (IBD) INDUCES INNATE IMMUNE MEMORY IN THE BRAIN WITH LONG-LASTING EFFECTS ON HIPPOCAMPAL NEUROGENESIS

Ioannis Alexandros Gampierakis[1,2], Yassemi Koutmani[1], Ioannis Charalampopoulos[2,3], Achille Gravanis [2,3], Katia P. Karalis [1,4]

1Center for Experimental Surgery, Clinical and Translational Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece. 2Department of Pharmacology, School of Medicine, University of Crete, Heraklion, Greece. 3Institute of Molecular Biology & Biotechnology (IMBB), Foundation of Research & Technology Hellas (FORTH), Heraklion, Crete. 4Endocrine Division, Children's Hospital, Harvard Medical School, Boston, MA, USA

john.gamp@yahoo.gr

Aims: Changes in microglia and neural stem cells activation in the hippocampus may underlie mood disorders and cognitive impairments described in Inflammatory Bowel Disease (IBD) patients. Repetitive and chronic peripheral inflammation alters the function of microglia, induces innate immune memory and negatively regulates hippocampal neurogenesis.

Methods: The dextran sodium sulfate (DSS) mouse model of IBD was used. Acute DSS colitis was induced by DSS administration in the drinking water for 4 or 7 days in 10-11 weeks old C57Bl6 mice. Chronic DSS colitis was induced by administration of DSS for multiple cycles and neurogenesis was assessed by BrdU administration and immunohistochemical analysis using a number of cell type specific markers. Immunobloting and qRT-PCR were performed to recapitulate acute and chronic colitis-specific features.

Results: During acute DSS colitis hippocampal microglia was gradually "trained" and became "tolerant". Microglia tolerance in DSS colitis was accompanied by a ramified non activated morphology, increased expression of the anti-inflammatory enzyme Arginase-1 in the hippocampus and enhanced hippocampal neurogenesis. Interestingly, the "tolerant" microglia was still present in the hippocampus of mice with chronic DSS colitis and induced a neuroprotective effect on newborn neurons. However, deficits in the migration pattern of newborn neurons were present. This could impact the functional integration of newborn neurons and alter the neuronal activity of the hippocampus with debilitating effects on mood and cognition.

Conclusions: Our findings indicate that the impact of experimental colitis in microglia and adult hippocampal neurogenesis could explain the reported cognitive and mood dysfunction in IBD patients.

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P219

MIRK/DYRK1B MINIBRAIN KINASE INDUCES CELL CYCLE EXIT AND NEURONAL DIFFERENTIATION IN VITRO AND IN VIVO AND MARKS EMBRYONIC AND ADULT NEUROGENESIS

Kokkorakis N.[1], Politis PK.[2], Masouti E.[1], Matsas R[1]. and Gaitanou M.[1]

1Laboratory of Cellular and Molecular Neurobiology-Stem Cells, Hellenic Pasteur Institute. 2Center of Basic Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece

nkokkorakis@pasteur.gr, mgaitanou@pasteur.gr

Aim: Our studies have implicated for the first time Mirk/Dyrk1B kinase in cell cycle exit and neuronal differentiation of Neuro2A cells suggesting a similar role for NPCs. Our aim is to elucidate the role of Dyrk1B in neurogenesis applying gain-of-function studies in vitro and in vivo.

Methods: Unilateral in ovo electroporation was performed in E2 chick spinal cord for Dyrk1B/GFP and GFP following by subsequent analysis at E4 by immunohistochemistry. Dyrk1B expression was investigated in the embryonic/adult chick and mouse CNS using immunohistochemistry, in situ hybridization and Western Blot analysis.

Results: Forced Dyrk1B expression in E2 chick spinal cord reduces by 2.3-fold BrdU incorporation and decreases PH3, Prox1 and Sox2 expression by 10, 4.9 and 1.5-fold respectively. Moreover, Dyrk1B+/GFP+ cells showed a neuronal fate phenotype, as indicated by increased Pax3 and Pax7 by 2.3 and 1.9-fold respectively and increased Nkx6.1, Islet-1, Doublecortin and βIII-tubulin by 1.9, 2.1, 1.4 and 1.2-fold respectively. In E4 chick spinal cord endogenous Dyrk1B is expressed by cycling neuronal progenitors and by differentiated motor neurons. In addition Dyrk1B protein is decreased during embryonic chick CNS development. In E12.5 mouse CNS, Dyrk1B is expressed both by cycling neuronal progenitors and by differentiated neurons. Moreover, Dyrk1B is expressed in the adult mouse cortex and hippocampus. Especially Dyrk1B is expressed by all along the neuronal lineage of adult dentate gyrus, suggesting a major role in embryonic and adult neurogenesis.

Conclusions: Mirk/Dyrk1B induces cell cycle exit and neuronal differentiation in vitro and in vivo and marks embryonic and adult neurogenesis.

We acknowledge support of this work by the project “Infectious, autoimmune and neurodegenerative diseases: study of the pathogenetic mechanisms and development of diagnostic, prognostic and therapeutic approaches” (MIS 5002486) which is implemented under the “Action for the Strategic Development on the Research and Technological Sector”, funded by the Operational Programme “Competitiveness, Entrepreneurship and Innovation” (NSRF 2014-2020) and co-financed by Greece and the European Union (European Regional Development Fund).

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POSTER SESSION 2

P220

EFFECTS OF PACAP FRAGMENTS (PACAP3-38 AND PACAP5-38) IN ISCHAEMIC RETINOPATHY

Szabo E[1], Vaczy A[1], Kovacs K[2], Kovari P[1], Reglodi D[1], Toth G[3], Atlasz T[1,4]

1Dept. of Anatomy, MTA-TKI PACAP Research Group, Medical School, University of Pecs, Pecs, Hungary. 2Dept. of Biochemistry and Medical Chemistry, Medical School, University of Pecs, Pecs, Hungary. 3Dept. of Medical Chemistry, University of Szeged, Szeged, Hungary. 4Dept. of Sportbiology, University of Pecs, Pecs, Hungary

szaboedina90@gmail.com

Introduction: Intravitreal PACAP38 and 27 are neuroprotective in different retinal injuries, including ischemia induced by bilateral common carotid artery occlusion (BCCAO). We proved that PACAP passes through ocular barriers and so, retinoprotection can be achieved also by eye drops. PACAP is degraded by dipeptidyl-peptidase IV to PACAP3–38 or 5–38, which have antagonistic properties. Therefore, it was of interest to examine whether topical application of these fragments worsens ischemic retinal injury that could interfere with future therapeutic applications.

Methods: Right eyes were treated with PACAP3-38 or 5-38 eye drops. Retinas were processed for morphometric and biochemical analysis.

Results: BCCAO resulted in severely reduced thickness in retinal layers, while histological and molecular examinations did not show any, either ameliorating or aggravating, effect of PACAP3-38 and -5-38.

Conclusion: Our results show that the degradation after topical application of PACAP38 or 27 does not lead to destructive fragments that could interfere with the retinoprotective treatment.

This work supported by NKFIH FK129190, GINOP-2.3.2-15-2016-00050”PEPSYS”, KTIA_13_NAP-A-III/5,PTE-AOK KA Research Grant (KA-2017-15), MTA-TKI 14016, Bolyai Janos Scholarship, EFOP-3.6.3-VEKOP-16-15 2017-00008, UNKP-18-4-PTE-364, UNKP-18-2-I-PTE-199, UNKP-16-4-IV, New National Excellence Program of the Ministry of Human Capacities, Centre for Neuroscience, 20765-3/2018/FEKUTSTRAT.

P221

SALIVARY PROTEOME ANALYSIS OF PACAP KO AND WILD TYPE MICE

Ádám Rivnyák[1], János Schmidt[2], László Márk[2], Péter Kiss[1], Dorottya Balogh[1], István Göcző[1], Dóra Reglődi[1]

1University of Pécs Medical School, Department of Anatomy, MTA-PTE PACAP Research Team. 2University of Pécs Medical School, Department of Biochemistry and Medical Chemistry, Hungary

rivnyakadam@gmail.com

PACAP (Pituitary adenylate cyclase-activating polypeptide) is an endogen neuropeptide with widespread biological effects. It acts mainly by activating the PKA-CREB pathway by increasing the level of cAMP. The peptide is present in several tissues with known physiological and cytoprotective effects.

PACAP also affects the secretion of exocrine serous glands such as the tear glands, salivary glands and the pancreas. Also immunohistochemical studies have shown the presence of PAC1 receptors in the salivary glands. In animal experiments the exogenously administered PACAP stimulates the amount of secretion of the above mentioned serous glands and the excretion of several factors. Based on these, we hypothesized that PACAP may also affect the protein composition of saliva.

To confirm our hypothesis, we analysed the saliva of PACAP KO and wild mice with liquid chromatography mass spectrometry (LC-MS). This method is suitably sensitive for detecting small protein concentrations and for qualitative and quantitative comparative studies. We assorted the secreted proteins, which had signal peptide. The secreted proteins, which had more than 2 fold change ratio were further analysed with STRING v11.0.

During our measurements hundreds of proteins were identified from the saliva samples. In the two groups, we have found significant differences in the level of 56 proteins and 20 of these had signal peptide. Among the 20 secreted protein, 11 was downregulated in knockout mice. These proteins were grouped by STRING based on GO Biological Processes database. The most significant changes were in the processes connected to the mucosal immune system and antimicrobial response.

Based on our findings, we can assume that PACAP has an effect on the salivary composition and may also play role in the immune system of the oral cavity due to the differences in the presence of proteins like lactotransferrin and myeloperoxidase. We already started to examine the microbiome of the oral cavity of PACAP knock-out and wild type mice.

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P222

INVESTIGATION OF PAC1 RECEPTORS IN HEALTHY AND PATHOLOGICAL HUMAN CORNEAS

Vicena V[1], Bárdosi A[2], Reglődi D[1], Juhász T[3], Módis L[4]

1Dept. of Anatomy, University of Pecs, Center for Neuroscience, Pecs, Hungary,MTA-TKI PACAP Research Group. 2Center for Histology, Cytology and Molecular Diagnostics, Trier, Germany. 3Dept. of Anatomy, University of Debrecen, Debrecen, Hungary. 4Ophthalmology Clinic, University of Debrecen, Debrecen, Hungary.

vicena.viktoria@gmail.com

Introduction: PACAP is a widespread neuropeptide with diverse physiological functions. It exerts general cytoprotective effects, thus playing a role in regeneration processes. This effect has been proven in vitro and in animal experiments in vivo, for both endogenous and exogenous PACAP. PACAP occurs in the ocular tissues and it also has protective effects in the cornea: it stimulates corneal regeneration, stimulates tear secretion and in gene deficient animals increased keratinization and corneal blurring can be observed. However, no human data are known. Our aim was to investigate the PAC1 receptor, in human corneal samples and to examine its changes in corneal diseases.

Methods: Human corneas removed during surgical procedures were processed for routine histological investigaton and PAC1 receptor immunohistochemistry, PCR and Western blot. The PAC1 receptor-expressing keratocytes in the corneal stroma were counted in standard areas and were compared using t-test.

Results: We showed that PAC1 receptor is expressed in the basal layers of the corneal epithelium and in the endothelium in all cases. In normal corneas no or minimal staining was observed in the stroma, while in re-grafts and other inflammatory conditions, significant increases in the number of PAC1 receptor expressing stromal keratocytes were observed. Molecular biological methods confirmed the presence of the peptide and its specific receptor.

Conclusion: Our results show that PAC1 receptor is expressed in the corneal epithelium and endothelium, while the receptor expression increases in inflammatory conditions in the stromal keratocytes. This suggests that the PACAP/PAC1 receptor pathway plays a significant role in regeneration processes.

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P223

NEUROPROTECTIVE EFFECT OF KYNURENIC ACID AGAINST EXCITOTOXICITY CAUSED BY N-METHYL-D-ASPARTATE

Gyula Jenei[1], Emma Balog[1], Judit Herédi[1], Levente Gellért[1], Anikó Magyariné Berkó[1], Zsolt Kis[1], László Vécsei[2,3], Etsuro Ono[4], József Toldi[1]

1Department of Physiology, Anatomy and Neuroscience, Faculty of Science and Informatics, University of Szeged, Szeged, Hungary. 2Department of Neurology, Faculty of Medicine, University of Szeged, Szeged, Hungary. 3MTA-SZTE Neuroscience Research Group, University of Szeged, Szeged, Hungary. 4Department of Biomedicine, Graduate School of Medical Sciences, Kyushu University Fukuoka, Japan; Center of Biomedical Research, Research Center for Human Disease Modeling, Graduate School of Medical Sciences, Kyushu University Fukuoka, Japan.

jeneigyuszi333@gmail.com

Aims: Kynurenic acid (KYNA), one of the main product of the kynurenine pathway originating from tryptophan metabolism, is considered to be neuroprotective. This effect is generally attributed to its antagonistic action on N-methyl-D-aspartate (NMDA) receptors. Our aim was to investigate the neuroprotective effect of KYNA using acute brain slices from C57BL/6J mice.

Methods: An excitotoxicity model was applied to examine the cell damage caused by different doses of NMDA. The neuroprotective effect of KYNA was assessed with biochemical (lactate-dehydrogenase (LDH) assay) and histological tools (Cresyl Violet staining, NeuN immunolabeling).

Results: In our experiments we used four doses of NMDA (10, 25, 50 and 100 µM) for the treatment of acute brain slices. Increasing concentration of NMDA treatment resulted in dose dependent release of LDH. Since the treatment with 100 µM NMDA caused massive cell damage on hippocampal neurons, 50 µM NMDA was chosen for our subsequent experiments. Both Cresyl-violet staining and NeuN immunolabeling showed that the CA1 region of the hippocampus is more sensitive to the neurotoxic effect of NMDA than the CA3 region. Neuroprotective effect of KYNA was tested at different concentrations (40, 100, 200, 500 nM). The increasing dose of KYNA treatment showed a dose-dependent neuroprotective effect on acute brain slices.

Conclusions: Taken together, these results provide important data about the neurotoxic property of NMDA and the dose-dependent neuromodulatory effect of KYNA.

Acknowledgments: This study was supported by grant GINOP 2.3.2-15-2016-00034 and co-financed by EFOP-3.6.1-16-2016-00008 grant and grant by MTA-SZTE Neuroscience Research group.

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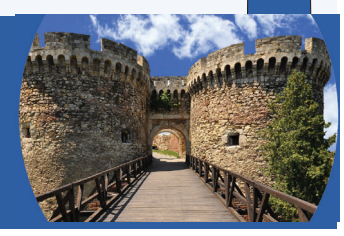

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P224

TRANSCRIPTOMIC ANALYSIS OF THE DORSOMEDIAL PREFRONTAL CORTEX IN SUICIDE VICTIMS

Fanni Dóra[1,2], Éva Renner[1], Miklós Palkovits[1], Árpád Dobolyi[2,3]

1Human Brain Tissue Bank Microdissection Laboratory, Semmelweis University, Budapest, Hungary. 2Laboratory of Neuromorphology, Department of Anatomy, Histology and Embryology, Semmelweis University, Budapest, Hungary. 3MTA-ELTE Laboratory of Molecular and Systems Neurobiology, Department of Physiology and Neurobiology, Eötvös Loránd University and the Hungarian Academy of Sciences, Budapest, Hungary

fanni.dora@gmail.com

Aims: Recent studies revealed that the resting state (RSN) network is a critical element in psychiatric disorders, especially in mood disorders. In the present study, we addressed RNA level changes in the dorsomedial prefrontal cortex (DMPFC), one of the major component of the RSN network, in relation to depression in suicide victims by RNA sequencing.

Methods: Subjects were assigned into three groups: control subjects without psychiatric disorders, depressed suicide victims, and suicides without any known signs of chronic depression. Brain tissue collections were performed within 2-10 hours after death.

Results: Cluster analysis suggested that the suicide and depressed suicide groups were quite similar, while both of them differ markedly from the control subjects. We found significant changes in the expression of over 200 genes between the control and suicide / depressed suicide groups. One of the differentially expressed genes between the control and suicide / depressed suicide groups was glial fibrillary acidic protein. Since this gene may have great importance as an indicator of astrocyte cell number, we validated its change by qRT-PCR and confirmed its reduction in suicide victims. Genes belonging to oxidative phosphorylation, endocrine cannabinoid signalling and cytokine receptor pathways were over-represented in suicide victims compared to controls.

Conclusions: The data imply extensive gene expressional alterations in the DMPFC related to depression and suicidal behaviour. The over-represented pathways may be involved in suicidal behaviour. The alterations suggest that the DMPCF has a role in these pathological conditions.

Support: EFOP 3.6.3-VEKOP-16-2017-00009, NKFIH NAP program 2017-1.2.1-NKP-2017-00002, and NKFIH-4300-1/2017-NKP_17.

P226

REGULATION OF MITOCHONDRIAL NCLX - EXCHANGER IN NEURONS BY CAFFEINE AND NEUROTRANSMITERS NOREPINEPHRIN AND VASOPRESSIN

Maya Rozenfeld, Ivana Savic Azoulay, Israel Sekler

Department of Physiology and cell biology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

mayagild@gmail.com

Aims: Mitochondrial Ca2+ influx is mediated by the mitochondrial Ca2+ uniporter (MCU) followed by Ca2+ efflux via the electrogenic Na+/Ca2+/Li+ exchanger (NCLX). NCLX-exchanger is activated in response to rise in mitochondrial Ca2+ levels and upregulated when phosphorylated by PKA. The Phosphodiesterase-2 (PDE-2) is a regulator of neuronal cAMP levels and when inhibited, cAMP accumulates and leads to enhanced activity of PKA. Here we ask if and how PDE-2 regulates NCLX when neurons are stimulated by Caffeine and neurotransmitters Norepinephrine (NE) and Vasopressin (VP).

Methods: We use live cell fluorescent imaging technique by employing specific fluorescent dyes that localize to the mitochondria.

Results: To study the physiological link between PDE-2 and NCLX in neurons, we used Bay-60-7550, a PDE-2-specific blocker and Caffeine, a non-specific PDE-2 inhibitor that also mediates Ca2+ fluxes from the ER to the mitochondria. We ask if the interaction of PDE-2 and NCLX is linked to neurotransmitters-dependent regulation of mitochondrial Ca2+. Our results show that Caffeine increases rates of mitochondrial Ca2+ efflux in WT but not in NCLX-KO hippocampal neurons. The effect of Caffeine was replicated upon application of Bay-60-7550 indicating that both block PDE-2. Bay-60-7550 also enhanced mitochondrial Ca2+ efflux when co-applied with neurotransmitters. We find a stronger effect of NE, VP when combined with Bay-60-7550 on upregulation of NCLX activity in neurons.

Conclusion: The results of our study highlight the importance of PDE-2-dependent regulation of NCLX and mitochondrial Ca2+ signaling in general.

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P227

LACTATE IS A NOVEL METABOLIC MEDIATOR BETWEEN ASIC1A AND MITOCHONDRIA

Ivana Savic Azoulay[1], Liu Fan[2], TL Xu[2], Israel Sekler[1]

1Department of Physiology and cell biology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel. 2Discipline of Neuroscience and Department of Anatomy, Histology and Embryology, Institute of Medical Sciences, Shanghai Jiao Tong University School of Medicine, Shanghai, China

savic.ivana1985@gmail.com

Aims: A major hallmark of neuronal metabolic activity is the buildup of lactic acid resulting in mild pH drop. In neurons, the decrease in extracellular pH can be sensed by acid-sensing ion channels - ASIC1a. Previous studies linked ASIC1a to pathophysiological insults in particular brain ischemia, which is followed by a very large pH drop. Here we ask how lactate affects mitochondrial metabolic activity and if its extra and intra cellular presence is related to ASIC1a activation.

Methods: We use live cell fluorescent imaging technique by employing ionic specific fluorescent dyes that localize in special cell departments such as cytosol or mitochondria.

Results: First, we show that racemic DL- lactate triggers robust ASIC1a dependent increase in both cytosolic and mitochondrial Ca^{2+} influx in neurons. Ca^{2+} transients are evoked exclusively when physiologically relevant L- lactate is present in the extracellular space, which indicates that there is a mechanism of ASIC1a activation by lactate other than chelating divalent ions, as shown in previous studies. We next show that L- lactate dependent acidification of intracellular space follows extracellular acidification. Cytosolic and mitochondrial Ca^{2+} signals are L- lactate dependent, as we demonstrate that when lactate transport is blocked, Ca^{2+} transients are lower. Finally, we show that Ca^{2+} propagation to mitochondria is NHE dependent, suggesting a significant role of this antiporter in ASIC1a activation pathway.

Conclusion: We here identify a novel link between ASIC1a and mitochondrial metabolic activity, mediated by propagating Ca^{2+}, Na^{+} and H^{+} signaling and controlled by a major metabolite lactate.

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P228

THE ROLE OF THE MITOCHONDRIAL SODIUM-CALCIUM EXCHANGER, NCLX, IN SYNAPTIC FUNCTION AND PLASTICITY IN HIPPOCAMPAL NEURONS

Alexandra Stavsky[1,2], Ohad Stoler[1,2], Ivana Savic[1,2], Yael Amitai[1,2], Ilya Fleidervish[1,2], Daniel Gitler[1,2], Israel Sekler[1,2]

1Department of Physiology and Cell Biology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel. 2Zlotowski Center for Neuroscience, Ben-Gurion University of the Negev, Beer-Sheva, Israel

sashkasss@gmail.com, stavskya@post.bgu.ac.il

Aims: Calcium is a pivotal player in synaptic transmission. Factors regulating presynaptic cytoplasmic calcium transients can influence release probability, vesicle recycling and energy consumption. Mitochondria have an important effect on these processes because they can sequester large quantities of calcium. The mitochondrial calcium steady-state is determined by the balance of calcium influx and efflux mechanisms. The mitochondrial sodium/lithium/calcium exchanger (NCLX) is a major pathway of calcium efflux. We sought to explore the effect of NCLX deletion on mitochondrial and synaptic calcium homeostasis, synaptic activity and plasticity.

Methods: We imaged calcium levels and synaptic release in cultured hippocampal neurons of NCLX knockout mice and wildtype mice using AAV2-based fluorescent sensors. Furthermore, we performed electrophysiological recordings in acute hippocampal slices.

Results: Our results demonstrate that deletion of NCLX leads to mitochondrial calcium overload under resting conditions and to partial depolarization of the mitochondrial membrane potential. We also observed a reduction in the mitochondrial calcium uptake. When examining activity-dependent cytoplasmic calcium transients in the presynaptic terminal, we observed that they were decreased; consequently, we measured weaker synaptic release, and direct assessment of the probability of synaptic release revealed it was lower. In agreement, we observed an enhancement in synaptic facilitation. Long term plasticity was also impacted: Schaffer collateral long term potentiation was abolished in slices from NCLX-KO mice.

Conclusions: These results suggest that NCLX is an important player in regulating mitochondrial calcium homeostasis and consequently cytoplasmic calcium, and that it thus plays a key role in regulating synaptic activity and plasticity.

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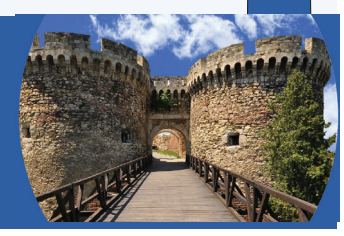

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P229

DISSOCIATED AMYGDALAR CULTURE: AN ALTERNATIVE MODEL TO STUDY NEURON-NANOMATERIAL INTERACTION

Secomandi N[1]*, Cellot G[1], Biagioni AF[1], Kostarelos K[2], Ballerini L[1]

1International School for Advanced Studies (SISSA/ISAS), Trieste, Italy. 2School of Medicine & National Graphene Institute, University of Manchester, United Kingdom

nsecoman@sissa.it

Aim: The aim of this study was to develop and characterize dissociated amygdalar cultures using electrophysiological and immunofluorescence techniques. Once obtained a reliable in vitro model, we exploited it to investigate the impact of nanomaterials on synapse regulation. In particular we focused on small graphene oxide (s-GO) nanosheet, a peculiar graphene-based material shown to interfere with presynaptic vesicle recycling.

Methods: Low-density cultures of isolated amygdalar neurons were prepared from postnatal rats (P9-P10) and used for experiments after 8-13 days in vitro (DIV). Whole cell patch clamp technique, both voltage and current clamp mode, was used to evaluate cell activity. Using immunofluorescence and confocal microscope we assessed the cell morphology of our preparations. Finally, to study the acute impact of s-GO nanosheets we locally delivered the nanomaterials using a picospritzer.

Results: Amygdalar neuronal networks were already electrically active at 8 DIV and the spontaneous post-synaptic current (sPSC) frequency did not change up to 13 DIV. However, in this time widow, we observed variation in passive properties, sPSC amplitudes and kinetics suggestive of neuron and synapse maturation. At 13 DIV we evaluated the short-term plasticity using paired pulse protocol in pairs of simultaneously monosynaptic connected neurons and we finally tested the acute impact of s-GO on synaptic release.

Conclusions: We developed amygdalar cultures characterized by maturation processes. Unitary synaptic interactions where mostly GABAergic in our recording conditions and characterized by short term depression. Regardless these features, we additionally show that amygdalar basal synaptic activity can be transiently regulated by s-GO.

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P230

PHARMACOLOGICAL TARGETING OF VTA DOPAMINERGIC NEURONS IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

La Barbera L.[1,2,3], Nobili A.[1,3], Latagliata E.C.[1], Cutuli D.[1], Krashia P.[1,2], Vedele F.[1,2], D'Amelio M.[1,3]

[1]Department of Experimental Neurosciences, IRCCS Santa Lucia Foundation, Rome, Italy. [2]Department of Systems Medicine, University of Rome 'Tor Vergata', Rome, Italy. [3]Department of Medicine, University Campus Bio-medico, Rome, Italy

livia.labarbera@gmail.com

We recently demonstrated that in the Tg2576 mouse model of Alzheimer's Disease (AD) the Ventral tegmental area (VTA) dopaminergic neurons degenerate. Degeneration occurs prior to Aβ-plaque deposition, tau tangles or any sign of cortical or hippocampal neuronal loss. The resulting dopamine deprivation in projection areas leads to memory and reward deficits reminiscent of AD, whereas levodopa could rescue these deficits in Tg2576 mice. Here, we investigate the hypothesis that the degeneration of dopaminergic neurons in Tg2576 is related to increased activity of the tyrosine kinase c-Abl.

Aims: Our aim was to examine the ability of Nilotinib, a c-Abl inhibitor, to block/delay degeneration in Tg2576 dopamine neurons, with the aim of eventually preventing cognitive and non-cognitive deficits. Nilotinib was earlier shown to reverse the loss of dopaminergic neurons in Parkinson's disease (PD) models, to improve cognitive/motor performances via autophagic degradation of β-amyloid and α-synuclein in models of AD and PD, respectively, and to reduce disease-related biomarkers in PD patients.

Methods: We chronically treated Tg2576 mice with Nilotinib (1 mg/kg, on alternate days), starting before the onset of VTA neuronal loss. We analyzed Nilotinib efficacy by stereological cell count of dopaminergic neurons, hippocampal microdialysis of dopamine outflow and behavioral testing.

Results: Nilotinib treatment: i) reduced VTA neuronal loss, ii) increased dopamine outflow in the hippocampus and iii) improved cognitive abilities.

Conclusions: These data suggest that the neuroprotection of VTA dopaminergic neurons in Tg2576 mice can postpone the onset of AD, demonstrating their importance as novel therapeutic targets.

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P231

EFFECT OF SMALL SYNTHETIC COMPOUNDS ON BIOCHEMICAL PROPERTIES OF PRION AND PRION-LIKE PROTEINS

Bhattacharya A[1], Pepe A[5], Pesapane A[4], Nitsch L[1], Montuori N[4], Lavecchia A[5], Zurzolo C[5], Sarnataro D[1],[4]

1Department of Molecular Medicine and Medical Biotechnologies, University of Naples "Federico II", Naples, Italy. 2Department of Translational Medical Sciences, University of Naples "Federico II". 3Department of Pharmacy, "Drug Discovery" Laboratory, University of Naples "Federico II". 4Ceinge-Biotecnologie Avanzate scarl, Naples, Italy. 5Institut Pasteur, Unité de Trafic Membranaire et Pathogénèse, Paris, France

antaripa1210@gmail.com

Cellular prion protein (PrPC) is a glycosylphosphatidylinositol (GPI) anchored-protein that can misfold into the pathogenic isoform PrPSc (scrapie), the causative agent of prion disease. PrPSc is amyloidogenic and its formation is related to the expression and intracellular localization of PrPC. PrPc was found to be regulated by synthetic inhibitors of a non-integrin receptor protein called 37/67 kDa LR, are able to influence both LR/PrP interaction and degradation of the receptor itself. Previous studies showed that 37/67 kDa LR may play a role in Alzheimer's disease. Hence modulation of 37/67 kDa LR could affect Aβ cytotoxicity and its release from cells, which highlights the importance of these synthetic inhibitors.

To detect whether Amyloid-β aggregation can be affected, we decided to inspect the impact of synthetic molecules on prion-like proteins (APP, Tau).

To analyze the effect of the synthetic molecules on PrP, APP, and Tau indirect immunofluorescence, co-immunoprecipitation assays were performed in neuronal cells. We have found that small compound treated GT-1 cells showed a significant reduction of both APP and Tau levels where the PrPC appeared stable on the plasma membrane. To figure out through which pathway the APP protein degrades after the drug treatment, we performed biochemical assays using NH4Cl to block the lysosomal function and Chloroquine to inhibit the autophagic flux. We noticed an increased amount of APP accumulation in NH4Cl and Chloroquine treated cells rather than controls, suggesting autophagosomal-lysosomal pathway degradation for APP.

Our results demonstrate that the synthetic compounds are able to regulate APP, PrP receptor trafficking and degradation.

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P232

EXPLORING HYBRID NETWORKS MADE BY NEURONS AND PROGENITORS CELLS

Teresa Sorbo, Mattia Musto, Laura Ballerini
SISSA International School for Advanced Studies, Trieste Italy

tsorbo@sissa.it

Aim: This work exploits neurons derived from rat pluripotent progenitor cells (NPCs) to investigate in vitro their interplay with post-mitotic hippocampal neurons in a mixed culture. In particular their integration in synaptic circuits since NPCs have been proposed in the design of neuro-restorative therapy.

Methods: NPCs, isolated from rat's embryo and expressing GFP, are cultured alone or 1:1 with primary neurons isolated from P3 rats' hippocampi. Thus, we studied the mixed culture neuronal network after 2 weeks of in vitro growth by single cell, whole-cell patch clamp electrophysiology and by immunofluorescence microscopy.

Results: NPCs explored under voltage clamp mode, showed low spontaneous post-synaptic currents (PSCs) frequency, mostly of GABAergic nature. When in mixed (with post natal neuron) cultures, NPCs displayed significant higher PSCs frequency characterized by a majority of AMPA events. By pair recordings we show in mixed cultures the appearance of AMPA synapses in NPCs pairs. The dynamic regulation of GABAergic phenotype in mixed cultures was also supported by GABA immunostaining. We further dissected the mechanistic role of neuronal electrical activity and glial signaling mediated by microvesicles (MVs) in such changes.

Conclusions: NPCs have the capacity to synaptically interact with post-mitotic hippocampal neurons contributing to network activity in mixed cultures. Electrical activity together with astrocytes-derived MVs affect NPCs maturation and the expression of the GABAergic phenotype. This indicates the crucial role of mature neurons and astrocytes in dictating NPCs development and, on the other hand, highlights NPCs ability to sense diverse signaling form the synaptic network activity and microenvironment.

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POSTER SESSION 2

P233

CALCIUM-INDEPENDENT PHOSPHOLIPASE A2-A (IPLA2B) EXACERBATES SECONDARY INJURY VIA LYSOPHOSPHATIDIC ACID (LPA) IN SUBACUTE SPINAL CORD INJURY

Sho Fujiwara[1], Yu-ichiro Ohnishi[1], Shinzawa Koei[2], Hirofumi Sugano[1], Nobuhiko Nakajima[1], Haruhiko Kishima[1]

1Department of Neurosurgery, Osaka University Graduate School of Medicine, Osaka, Japan. 2Department of Molecular Biology and Biochemistry, Osaka University Graduate School of Medicine, Osaka, Japan

momo4893002@yahoo.co.jp

Introduction: Central nervous system includes various membrane phospholipids and maintains these lipids by metabolic enzymes. Phospholipase A2 (PLA2) is a diverse family of enzymes that hydrolyze glycerophospholipids to produce free fatty acids and lysophospholipids. These products are precursors of mediators in tissue damage and inflammation. PLA2G6 gene (iPLA2β) was causative of the hereditary neurodegenerative disease. PLA2G6 gene knockout (KO) mouse is known as the human neurodegenerative disease model, which present pathological changes of the posterior horn of spinal cord.

Aim: We investigated the pathological involvement of iPLA2β in the sub-acute spinal cord injury (SCI).

Methods: We performed moderate contusion injury at Th10 for PLA2G6 KO and wild-type (WT) mice in 8 weeks olds. The inhibitor and antibody for iPLA2β was continuously administered into the intrathecal space of WT mouse. Locomotor function was evaluated until 4 weeks after SCI using the Basso Mouse Scale. Histology and western blotting was examined. Lipid metabolism at injury epicenter one week after SCI was analyzed using mass spectrometry.

Results: Locomotor function of KO mouse was significantly recovered in comparison with WT. The inhibitor and antibody for iPLA2β attenuated the locomotor dysfunction of WT mouse after SCI. Histology revealed that the cavity and demyelination of the injury site was significantly reduced in KO mouse. Mass spectrometry presented that LPA derived from iPLA2β were significantly decreased.

Conclusion: This study clarified that iPLA2β exacerbates secondary injury via LPA in subacute SCI.

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P234

EVALUATION OF THE PROTECTIVE EFFECT OF WEISHENG-TANG BASED DONGEUIBOGAM ANALYSIS USING ISCHEMIC STROKE MICE MODEL

Min Jae Kim, Byung Tae Choi, Jin Ung Baek, Seo-Yeon Lee, Hwa Kyoung Shin

1Department of Korean Medical Science, School of Korean Medicine, Pusan National University, Yangsan, Gyeongnam, Republic of Korea. 2Korean Medical Science Research Center for Healthy-Aging, Pusan National University, Yangsan, Gyeongnam, Republic of Korea. 3Graduate Training Program of Korean Medicine for Healthy-Aging, Pusan National University, Yangsan, Gyeongnam, Republic of Korea

dpxls0@pusan.ac.kr

Aim: Stroke is one of major causes of death and long-term disability, but stroke is not completely treated. In Dongeuibogam, an ancient literature on Korean medicine, many medicinal herbs and formulas were used to treat the symptoms related with stroke. In this study, we selected two Korean herbal medicine formulas, Weisheng-tang and Togxuewan, from Dongeuibogam through text-mining, and evaluated the protective effect on ischemic stroke using focal cerebral ischemic mouse model.

Methods: Focal cerebral ischemia was induced by photothrombotic cortical ischemia. Infarct volume, brain edema, neurological deficits, wire-grip and Evans blue leakage were evaluated. Immunofluorescence staining for endothelial cell, tight junction proteins and protease-activated receptor-1 (PAR-1) was performed in brain tissues after ischemic injury.

Results: Pretreatment of Weisheng-tang significantly reduced infarct volume and edema and improved neurological and motor functions, but Togxuewan did not. In addition, Weisheng-tang dose-dependently (30, 100, and 300 mg/kg) decreased brain infarct and edema, and recovered neurological and motor deficit. Weisheng-tang pretreatment significantly decreased blood-brain barrier (BBB) breakdown as measured by Evans blue leakage after focal cerebral ischemia. Immunohistochemical analysis reveals that zonula occludens-1 (ZO-1) expression in ipsilateral site was significantly increased in Weisheng-tang pretreated mice. Moreover, high level of PAR-1 was observed in ischemic mice, but PAR-1 immunofluorescence was decreased in Weisheng-tang pretreated mice.

Conclusions: These results indicate that Weisheng-tang identified by text-mining technique has the protective effects on ischemic brain injury, and suggest the possible application for potential stroke patients especially in elder person.

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P235

CELLULAR, MOLECULAR AND TRANSCRIPTOMIC ANALYSIS OF THE EFFECTS OF STIGMASTEROL ON RAT BRAIN NEURONAL DEVELOPMENT AND MIGRATION

Haque MN[1,2], Moon IS[1,2]

1Medical Institute, College of Medicine, Dongguk University, Gyeongju, Republic of Korea. 2Department of Anatomy, College of Medicine, Dongguk University, Gyeongju, Republic of Korea

moonis@dongguk.ac.kr

Aim: To investigate the neuromodulatory effects of sigmasterol (ST), a natural phytosterol on the development of central nervous system neurons and the molecular bases of these effects in primary hippocampal neurons.

Methods: Total RNA of rat embryonic brain neuronal cultures (DIV 12) were sequenced and ST-affected key genes for neuronal development were identified using bioinformatics tools and their upregulations were confirmed by Western blot (WB) and immunocytochemistry (ICC). In vitro neurosphere (E14 rat cortical neurons) migration assays were used for the effects of ST on neuronal migration. For this purpose, neurospheres were produced by culturing rat (Sprague-Dawley) E14 cortical neurons.

Results: Total RNA-seq analysis showed that ST induced immediate early genes (IEGs) related to central nervous system (CNS) development (neurite outgrowth or synaptic transmission). In a Venn diagram for CNS development Gene Ontologies (GOs) (i.e., axon development, dendrite development, modulation of synaptic transmission), Reln emerged as a central player in these processes, and highly interconnected 'hub' genes, including Dcx, Egr1, Ntrk2, and Slc24a2, were revealed by gene co-expression networks. WB and ICC showed that ST upregulates Cdc42-Arp2/3 and Erk1/2-Creb signaling and thus induces the formations of mushroom-type spines and glutamatergic excitatory synapses. Finally, ST upregulated Reelin (Reln) and its downstream signaling molecules like phospho-JNK (c-Jun N-terminal kinase), doublecortin (DCX) and dynein heavy chain (DHC) in migratory neurons.

Conclusions: This study indicates that ST upregulates genes for neuritogenesis, synaptogenesis, and neuronal migration suggesting ST be a potential resource for improving brain functions.

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P236

DIFFERENTIAL EFFECTS ON HIPPOCAMPAL NEUROGENESIS AFTER SINGLE OR MULTIPLE SESSIONS OF THALAMIC STIMULATION

Farah Chamaa[1], Ziad Nahas[2,3], Nayef Saade[1] and Wassim Abou-Kheir[1]

1Department of Anatomy, Cell Biology and Physiological Sciences. 2Department of Psychiatry, Faculty of Medicine, American University of Beirut Medical Center, Beirut, Lebanon. 3Department of Psychiatry, Medical School, University of Minnesota, Minneapolis, Minnesota, United States

fs36@aub.edu.lb, wa12@aub.edu.lb

Aims: Deep brain stimulation (DBS) provides substantial benefit for movement disorders. It is still unknown how DBS alters neural activity, but hippocampal neurogenesis may be one possible aspect. We have previously shown that single session of anteromedial thalamic nucleus (AMN) stimulation induces hippocampal-stem/progenitor cell proliferation in the dentate gyrus (DG). This study examines the long term effect of single compared to multiple sessions of AMN electrical stimulation in modulating hippocampal neurogenesis and in affecting exploration of the rats in the Y-maze behavioral test.

Methods: Adult male Sprague-Dawley rats received either single or multiple unilateral sessions of electrical stimulation in the right AMN. All groups received 5'-bromo-2'-deoxyuridine (BrdU) injections and were euthanized 4 weeks post-stimulation. The BrdU/NeuN-positive cells in DG were counted and the exploratory behavior of the rats were tested using the Y-maze.

Results: Single AMN electrical stimulation induced a 1.8-fold increase in hippocampal neurogenesis at 4 weeks post-stimulation. Multiple sessions of electrical simulation further increased neurogenesis to 3-folds higher. The Y-maze test showed that single electrical stimulation to the AMN enhanced the exploratory behavior of the rats at 4weeks post-stimulation while multiple sessions induced an early effect starting 7days after stimulation.

Conclusions: The current study presents an increase in hippocampal neurogenesis in response to single session of electrical stimulation in awake anesthesia-free rats. Additional effects were induced after multiple sessions of electrical stimulation for 6days. This reveals a translational behavioral enhancement of hippocampal-related skills following stimulation, specifically after multiple sessions which mimics clinical practice.

Funding Source: Lebanese National Council for Scientific Research (LNCSR)

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P237

DBCAMP PROTECTS THE NEURONS FROM HYPERGLYCEMIA-INDUCED NEURODEGENERATION-AN IN-VITRO STUDY

Rao MS, Smitha S

Department of Anatomy, Faculty of Medicine, Kuwait University, Kuwait

muddanna@hsc.edu.kw

Aims: Dibutyryl cyclic adenosine monophosphate (dBcAMP) is a cell-permeable synthetic analog of cyclic adenosine monophosphate (cAMP) known to acts as an intracellular second messenger. Present experiment was aimed to study the effects of dBcAMP on neurons and astrocyte in in-vitro hyperglycemic model of diabetes.

Methods: Primary cultures of the hippocampal cells from E18 day's hippocampus were grown for 10 days. These cultures were divided into control (C), hyperglycemic (HG), dibutyryl cyclic AMP (dBcAMP)), and hyperglycemia+dibutyryl cyclic AMP (HG+dBcAMP, n=6). C and dBcAMP cultures continued to grow in normal media. HG and HG+dBcAMP cultures were continued to grow in media containing high (100mM) glucose. dBcAMP and HG+dBcAMP cultures were treated with 10µM dBcAMP for one week. Cultures were immunostained for Tuj1 (neurons) and GFAP (astrocytes). Number of neurons and glial cells were quantified.

Results: Cell proliferation and cell viability were significantly decreased in HG compared to C ($p<0.01$) and it is increased in dBcAMP and HG+dBcAMP groups. Number of astrocytes and neurons were found to be significantly decreased in HG compared to C cultures ($p<0.01$). Increase in the number of neurons and astrocytes was confirmed by increase in Tuj1 and GFAP content by western blot analysis. Neurons and astrocytes in the cultures treated with dBcAMP had larger cell bodies and longer processes compared to control culture.

Conclusions: We conclude that dBcAMP protects the neurons from hyperglycemic effects, by increasing glial cell population. Hence dBcAMP may be a potential molecule to be considered in treatment of diabetic patients to prevent the neurodegeneration.

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P238

DEREGULATED AUTOPHAGY LEADS TO CHANGES IN SYNAPTIC FUNCTION IN AN IPSC-DERIVED MODEL FOR KOOLEN-DE VRIES SYNDROME

El Lewerissa, K Linda, A Verboven, M Frega, SHC van Gestel, T KleinGunnewiek, DA Koolen, BB de Vries, N Nadif Kasri

Department of Human Genetics and Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, Netherlands

elly.lewerissa@radboudumc.nl

Koolen-de Vries syndrome (KdVS) is a heterogeneous multisystem disorder characterized by developmental delay, intellectual disability, facial dysmorphisms, epilepsy, and congenital malformations in multiple organ systems. Loss-of-function mutations and atypical deletions restricted to the KANSL1 gene have been found in several KdVS patients. KANSL1 is a member of the nonspecific lethal complex that contains the histone acetyltransferase MOF, which acetylates histone H4 on lysine 16 (H4K16) to facilitate transcriptional activation. Our recent studies in flies and mice have shown that heterozygous loss of kansl1 leads to changes in gene expression related to synaptic transmission, and to a decrease in basal synaptic transmission and plasticity (Arbogast et al., 2017).

Here, we investigated the molecular mechanisms underlying the synaptic dysfunction in a human model of KdVS focusing on H4K16ac and its role in the regulation of autophagy, a cellular process controlling the degradation and recycling of proteins. Deregulation of autophagy has been linked to neurodevelopmental disorders.

Using several KdVS patient cell lines we found that under basal conditions autophagy is increased, both in induced-pluripotent stem cells (iPSCs) and induced-neurons (iNeurons) derived from KdVS patients. By investigating gene expression profiles that are associated with H4K16 acetylation, we found that SOD1 gene expression was down-regulated, leading to a subsequent increase in oxidative stress and autophagy. Increased autophagy in maturing KdVs iNeurons resulted in reduced synaptic density and AMPA receptor-mediated synaptic transmission.

Together our results show a role for KANSL1 in the regulation of autophagy-related gene transcription by H4K16 acetylation in human iPSCs and iNeurons.

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P239

THE ROLE OF AMOT AND YAP1 IN THE REGULATION OF DENDRITIC TREE COMPLEXITY AND CEREBELLAR FUNCTIONS

Katarzyna Rojek[1], Joanna Krzemień[1], Hubert Doleżyczek[2], Marcin Rylski[3], Leszek Kaczmarek[2], Jacek Jaworski[4], Tomasz Prószyński[1]

[1]Laboratory of Synaptogenesis, Nencki Institute of Experimental Biology, Warsaw, Poland. [2]Laboratory of Neurobiology, Nencki Institute of Experimental Biology, Warsaw, Poland. [3]The Medical Center of Postgraduate Education, Warsaw, Poland. [4]International Institute of Molecular and Cell Biology, Warsaw, Poland

k.rojek@nencki.gov.pl

Aims: The Amot-Yap1 complex plays a major role in the regulation of cell contact inhibition, cellular polarity and growth in many cell types. However, the function of Amot and Hippo pathway transcription co-activator Yap1 in the CNS remains unclear. Recent studies have demonstrated that in mature hippocampal neurons, Amot localizes to dendritic spines where it associates with synaptic protein, and regulates actin cytoskeleton. However, its function during neuronal development has not been studied.

Methods: Cultured primary neurons were used for RNAi experiments. For in vivo functional analysis we used Amot and Yap1 conditional KO mice. For deletion in single sparse neurons mice were injected low doses of AAV-CRE. For behavioral analysis we used rotarod, catwalk and foot fault tests.

Results: We demonstrate that Amot is a critical mediator of dendritogenesis in cultured hippocampal cells and Purkinje cells in the brain. Amot function in developing neurons depends on interactions with Yap1, which is also indispensable for dendrite growth and arborization in vitro. Conditional deletion of Amot or Yap1 in neurons leads to decreased Purkinje cell dendritic tree complexity, abnormal cerebellar morphology and impaired motor coordination. The ability of Amot and Yap1 to regulate dendritic growth depends on regulation of S6 kinase activity and phosphorylation of S6 ribosomal protein. Hence, suggesting that Amot and Yap1 control dendritic tree morphogenesis through a cross-talk with the PI3K/mTOR pathway, a known regulator of dendritogenesis.

Conclusions: We identify a novel role for the scaffold protein Amot and the Hippo pathway transcription co-activator Yap1 in dendritic morphogenesis.

This research was supported by the National Science Center grants: 2012/05/E/NZ3/00487 and 2015/19/N/NZ3/02346.

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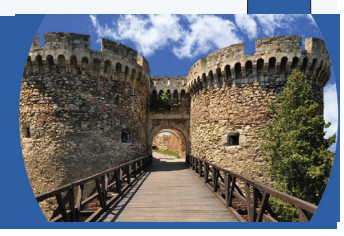

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P240

MOLECULAR AND CELLULAR BASIS OF REBOUND DEPOLARIZATION IN PYRAMIDAL NEURONS OF PREFRONTAL CORTEX

Przemysław Kurowski, Maciej Korczak, Magdalena Bujalska-Zadrozny

Laboratory of Physiology and Pathophysiology, Department of Pharmacodynamics and Pathophysiology, Medical University of Warsaw, Warsaw, Poland

przemyslaw.kurowski@gmail.com

Aim: Rebound depolarization (RD) is a form of membrane depolarization triggered in some neurons following hyperpolarization. Typically, a series of action potentials are evoked during RD plateau. RD converts an inhibitory signal arriving to the neuron into an excitation signal, which is subsequently synaptically transmitted to other cells. The nature of RD in cortical neurons has been tested for several years without satisfactory explanation. The purpose of our study was to identify the mechanisms that trigger RD.

Methods: Experiments were performed in synaptically isolated layer V mPFC pyramidal neurons in slices obtained from adult male rats. Recordings of membrane potential were performed in whole-cell current-clamp configuration.

Results: The key finding of our study is that following temporary hyperpolarization, two currents are concomitantly activated: 1. a low-threshold, persistent inward Na+ current that evokes RD; and 2. an outward K+ current through Ca2+-dependent K+ (type BK) channels that opposes Na+-dependent depolarization. These currents conceal each other in resting conditions, not allowing the emergence of RD. RD occurred when the outward K+ current through BK channels was abolished by the extracellular application of paxilline, by removing Ca2+ from either the extra- or intracellular solution, by activation of phospholipase C or protein kinase C. Furthermore, RD could be evoked by activation of several neurotransmitter receptors, among others by GABAB receptors.

Conclusions: Our results explain how RD arises in medial prefrontal cortex pyramidal neurons.

The study was supported by the National Science Centre, Poland (grant number: 2015/17/N/NZ4/02889) and the Medical University of Warsaw (grant number: FW5/PM1/18).

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P241

BITTER TASTE SIGNALLING IN GLIOBLASTOMA

Costa, AR., Gonçalves, I., Cascalheira, JF., Duarte, AC., Santos, CRA.

CICS-UBI - Health Sciences Research Centre, Universidade da Beira Interior, Covilhã, Portugal

anarfcosta1990@gmail.com

Aims: During their lifetime, 1 in 74 people will be diagnosed with CNS tumours. Glioblastoma multiforme (GBM; WHO grade 4) is the most common and most aggressive form of primary brain cancer. There are evidences that gene expression of bitter taste receptors (TAS2Rs), most likely associated with chemosensing, change in several neurological diseases. In humans, 25 genes encoding members of the TAS2Rs were identified as well as downstream functional effectors, and all are expressed in the brain. Therefore, the aim of this work was to analyse the expression of the taste transduction machinery in in vitro models of different GBM grades, and to examine its capacity to recognize bitter compounds with potential use for cancer therapy.

Methods: The mRNA and protein expression of the taste signalling pathway was evaluated in three in vitro models of different GBM grades (U-87MG, U-373MG and SNB19). Then, we assessed the taste signalling response to different brain-targeting bitter drugs by calcium imaging functional studies.

Results: We demonstrated that the different GBM cell lines differentially express mRNA and proteins involved in the transduction of bitter compounds signalling. Moreover, we identified ligands for the most representative TAS2Rs through glioblastoma cell stimulation with bitter compounds of therapeutic interest, like temozolomide and flavonoids, and the dose-response curves to each compound were determined.

Conclusions: These findings put in evidence an alternative pathway for the detection of bitter compounds that might be associated with chemoresistance in glioblastoma cells.

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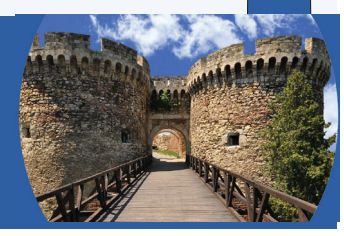

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P242

TAS2R14 REGULATES RESVERATROL TRANSPORT IN THE HUMAN BLOOD-CEREBROSPINAL FLUID

Duarte AC.[1], Gonçalves I, Santos J, Gallardo E, Rosado T, Costa AR, Quintela T, Santos CR

CICS-UBI – Health Sciences Research Centre, Universidade da Beira Interior, Covilhã, Portugal

anacduarte28@hotmail.com

Aims: The blood-cerebrospinal fluid (CSF) barrier, established by the choroid plexus, constitutes a unique interface between the blood and CSF, that monitors the composition of both fluids. Despite the well-recognised role of the blood-CSF barrier in impairing dangerous substances to reach the CSF, the mechanisms that operate at this barrier are still poorly understood. Bitter receptors, TAS2R, previously described in rat choroid plexus, display several ligands with pharmacological interest, as such resveratrol. This suggests a possible action of TAS2R in the choroid plexus to maintain the fluid's composition.

Methods: The expression of TAS2Rs was analyzed by RT-PCR, Western blot and immunofluorescence in HIBCPP cells. Moreover, calcium functional assays were performed, and resveratrol transport was assessed across HIBCPP monolayer. Resveratrol was quantified by high-performance liquid chromatography-diode array detector.

Results: The cells response to resveratrol occurred in a dose-dependent manner, as observed in calcium imaging assays. This response diminished when silencing TAS2R14 expression but not TAS2R39. Moreover, we assessed resveratrol transport across HIBCPP cells monolayer from the basolateral to the apical side. We observed resveratrol accumulation in the apical side, however at a lower concentration when cells were transfected with TAS2R14 siRNA.

Conclusions: Resveratrol bind and activate TAS2R14 in HIBCPP cells. Silencing TAS2R14 reduced resveratrol transport across the CP cells. Our findings suggest that TAS2R14 is the receptor for resveratrol present at the basolateral membrane of HIBCPP cells and modulates its transport from the peripheral circulation to the CSF.

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P243

METABOLIC SYNDROME AND BRAIN HOMEOSTASIS: FOCUS ON THE BLOOD-BRAIN BARRIER, CONSTITUTIVE AND REGENERATIVE NEUROGENESIS

Diotel Nicolas, Emmanuel Bourdon, Christian Lefebvre d'Hellencourt, Olivier Meilhac

Université de La Réunion, Institut National de la Santé et de la Recherche Médicale, UMR 1188, Diabète athérothrombose Thérapies Réunion Océan Indien, France

nicolas.diotel@univ-reunion.fr

A growing body of evidence suggests that metabolic syndrome (ex: obesity, hyperglycemia) is a putative contributor to several brain dysfunctions. Diabetes and/or obese patients actually appear to display impaired memory capacity and decreased brain plasticity. However, the understanding of the impact of metabolic syndrome and hyperglycemia on brain dysfunction is still poorly documented.

We consequently aimed at exploring the impact of metabolic syndrome/hyperglycemia on brain homeostasis and neurogenesis under constitutive and regenerative conditions using zebrafish. Thanks to the persistence of neural stem cells in Teleost, the zebrafish constitutes a relevant model to investigate constitutive and injury-induced neurogenesis in adult vertebrates.

Our results demonstrate that hyperglycemia and overweight impaired brain homeostasis. For instance, hyperglycemia promotes gene expression of proinflammatory cytokines in the brain and disturbs the expression of genes involved in the establishment of the blood-brain barrier (claudin 5a, zona occludens 1a and b). Strikingly, hyperglycemic fish also displayed a decrease in cell proliferation in most neurogenic niches throughout the brain, and brain repair mechanisms were blunted. We also investigated the impact of diet-induced obesity and our preliminary results tended to show a decreased neurogenesis, and impaired locomotor activity.

Taken together, these data offer new evidences highlighting the evolutionary conserved adverse effects of metabolic syndrome on neurogenesis, brain healing and behavior in zebrafish and opens a field of research for testing new pharmaceuticals.

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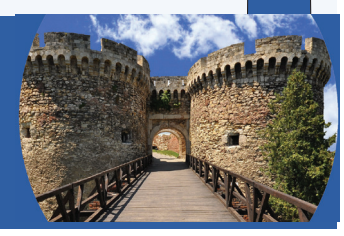

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P244

CHLORIDE TRANSPORT MODULATION IMPACTS THE RESPONSE OF HIPPOCAMPAL NEURONS TO OXYGEN-GLUCOSE DEPRIVATION AND REOXYGENATION

Rosana-Bristena Ionescu[1], Ioana Florentina Grigoras[1], Mara Ioana Iesanu[1], Diana Maria Chitimus[1], Robert Mihai Haret[1], Tudor Mihai[1], Bogdan Ianosi[2], Mihai Ceanga[3], Ana-Maria Zagrean[1]

1Division of Physiology and Neuroscience, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania. 2Department of Neurology, Division of Neurocritical Care, Medical University of Innsbruck, Innsbruck, Austria. 3Hans Berger Department of Neurology, Jena University Hospital, Jena, Germany

bristena.ionescu@gmail.com

Neuronal metabolic vulnerability can be studied *in vitro* using oxygen-glucose deprivation (OGD), resulting in alteration in ionic gradients and excitability-inhibition balance. Subsequently, intracellular chloride level shifts, changing the neuronal response to GABAA receptor activation from hyperpolarising to depolarizing in mature cells, and impacting on cellular viability. Also, the changes in intracellular chloride are depending on the chloride co-transporters (NKCC1 and KCC2) expression and activity.

In the present study we examined the effect of NKCC1-antagonist bumetanide, KCC2-antagonist DIOA, GABAA-antagonist gabazine or GABAA-agonist isoguvacine on the response of mature hippocampal neurons to OGD and reoxygenation in culture, by measuring cell viability.

Briefly, rat primary hippocampal cultures were exposed to 2h OGD +/- reoxygenation or control conditions after 7 days in vitro. Treatments were performed either during OGD or reoxygenation. Cellular viability was measured using the resazurin assay during 3h of reoxygenation.

Our results show that the decrease in cellular viability triggered by OGD exposure ($p<0.05$) was further accentuated by DIOA treatment during OGD and gabazine treatment during reoxygenation ($p<0.05$). Bumetanide treatment during OGD increased cellular viability when compared to nontreated OGD-exposed cultures ($p<0.05$).

In conclusion, pharmacological modulation of intracellular chloride level in hypoxia/ischemia and reoxygenation depends on the dynamic of chloride transport disruption and may provide new therapeutic strategies.

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POSTER SESSION 2

P245

SPATIAL INTERACTIONS BETWEEN THE IBA-1 (+) MACROPHAGES AND THE CGRP (+) DRG NEURONS

Cristina Stratan[1], Gisela Gaina[2], Roxana Gheorghe[1], Violeta Ristoiu[1]

1Department of Anatomy, Animal Physiology and Biophysics, Faculty of Biology, University of Bucharest, Bucharest, Romania. 2Faculty of Biology, University of Bucharest, Bucharest, Romania

cristina.stratan@gmail.com

Aims: Interactions between dorsal root ganglia (DRG) nociceptive neurons and immune cells are very important in pain transduction. In particular, after a spinal nerve ligation lesion resident Iba-1 (+) macrophages in the DRG form perineuronal rings which presumably sensitize them and contribute to increased pain. Our study aimed to assess the spatial interactions between the Iba-1 (+) macrophages and the small CGRP (+) DRG neurons after +/- silencing Iba-1 a cytoskeleton protein, which would alter macrophages' mobility and therefore their ability to form perineuronal rings.

Methods: Male Sprague-Dawley rats were assigned to one of the following groups: control (without injection), sham (without SNL, but with control injection), SNL and SNL/Iba-1 (injected with Iba-1 siRNA). Injected rats received 4 µl of 400 nM Iba1 siRNA or 400 nM scrambled siRNA/ PBS 0.2X into the lumbar 5 (L5) DRG. DRG sections have been prepared and spatial interaction between macrophages and neurons was analyzed immunohistochemically, using antibodies to Iba-1 (for macrophages) and to CGRP (for neurons).

Results: After SNL, macrophages displayed a clear activated profile marked by the presence of ruffles with a ring distribution around the DRG neurons, with a lesser prevalence around CGRP (+) neurons, but a marked tendency to surround the medium and large neurons. Silencing Iba-1 did not reduce the macrophages ability to form perineuronal rings, which nevertheless looked looser than without treatment.

Conclusions: The spatial distribution of the resident macrophages around small neurons in post-SNL DRG suggest a close communication between macrophages and the neuronal body, possibly mediated by chemical signaling.

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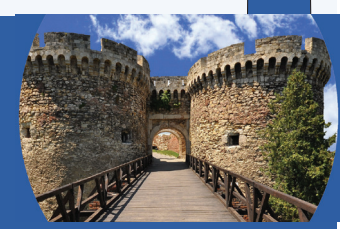

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P246

TRANS-RESVERATROL SUPPLEMENTED MATERNAL DIET IMPROVES THE EARLY NEUROLOGIC OUTCOME IN RAT OFFSPRING CONSECUTIVE TO PERINATAL ASPHYXIA

Mara Iesanu[1], Sebastian Isac[1], Anca Maria Panaitescu[1,2], Ana Spataru[1], Alexandra Totan[3], Natalia Cucu[4], Leon Zagrean[1], Ana-Maria Zagrean[1]

1Division of Physiology and Neuroscience, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania. 2Filantropia Clinical Hospital, Bucharest, Romania. 3Division of Biochemistry, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania. 4Association for Epigenetics and Metabolomics, Bucharest, Romania

iesanu_mara@yahoo.com

Dietary intake during pregnancy was shown to influence child neurodevelopment and cognitive function. Trans-resveratrol (tRESV) has been reported to exert a plethora of health benefits, being easily accessible as a maternal dietary supplement in perinatal asphyxia (PA).

Our study is aiming to explore the benefit of tRESV enriched maternal diet on early neurological outcome and to identify epigenetic controlling mechanisms of the brain inflammation and injury related to PA.

Asphyxia was induced in postnatal day 6 Wistar rats whose mothers received either standard or tRESV enriched diet, by exposure for 90 min to a hypoxic-hypercapnic environment. Pups were sacrificed and the hippocampi were isolated and collected at 24 and 48h after the exposure. Hippocampal neuroinflammation was assessed by ELISA measurement of TNFα and IL-1b levels, while neural injury was quantified by determining the S-100B concentration. The expression of 5 different microRNAs as epigenetic markers of hippocampus response to PA was determined 24h post-asphyxia. Seizure burden was assessed by the cumulative number of loss of righting reflex (LRR) over a 2h post-exposure period. Moreover, the hippocampal metabolic activity was assessed using resazurine test 24h after PA.

The results indicate that neural adaptation to PA is epigenetically controlled and that tRESV reduces asphyxia-related neuroinflammation and neural injury, increasing at epigenetic level the ischemia tolerance, reducing the seizure burden and increasing the metabolic activity.

The data obtained supports a significant protective effect of maternal tRESV supplementation on the offspring's hippocampal vulnerability to PA.

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P247

MELITTIN DISTINCTLY REGULATES SUR1- OR SUR2-COUPLED KIR6.2 PORE-FORMING SUBUNITS EXPRESSION IN RAT DORSAL ROOT GANGLIA NEURONS

Beatrice Mihaela Radu[1,2], Adela Banciu[3], Daniel Dumitru Banciu[3], Diana Ionela Dumitrescu[4], Cosmin Cătălin Mustăciosu[5], Călin Mircea Rusu[5], Mihai Radu[5]

1University of Bucharest, Faculty of Biology, Department of Anatomy, Animal Physiology, and Biophysics, Bucharest, Romania. 2Life, Environmental and Earth Sciences Division, Research Institute of the University of Bucharest (ICUB), Bucharest, Romania. 3Department of Bioengineering and Biotechnology, Faculty of Medical Engineering, University Politehnica of Bucharest, Bucharest, Romania. 4Institute for Diagnosis and Animal Health, Bucharest, Romania. 5'Horia Hulubei' National Institute of Physics and Nuclear Engineering, Department of Life and Environmental Sciences, Bucharest-Magurele, Romania

beatrice.radu@bio.unibuc.ro

Aims: ATP-sensitive potassium (K(ATP), i.e. Kir6.1 and Kir6.2) channels are expressed in primary afferent neurons and their are altered upon peripheral nerve injury. As Kir6.2 channels are considered promising therapeutical targets in peripheral pain, the goal of our study was to test the effect of melittin, the active compound of bee venom, on these channels.

Methods: Primary cultures of dorsal root ganglia (DRG) neurons were obtained from adult male Wistar rats. Neurons were treated with 0.1, 1 and 5 μM melittin, for 0.5, 1, 3, 5, 7 and 18 hours, and the cell viability was tested by the MTT assay. After 18 hours of melittin treatment, Kir6.2, Sur-1, Sur-2 mRNA levels were quantified by qRT-PCR by Gapdh mRNA normalization and immunofluorescence analysis of Kir6.2, Sur-1, Sur-2 expression and co-localisation in DRG neurons was done.

Results: Melittin (1 and 5 μM) decreases the neurons viability at different timepoints up to 40% upon 18 hours of treatment. Melittin at low doses (0.1 μM) downregulates Kir6.2 (0.85-fold) and Sur-1 (0.76-fold), while upregulates Sur2 (1.5-fold), and at medium doses (1 and 5 μM) upregulates Kir6.2 (1.2-fold, 1.4-fold) and Sur-2 (1.38-fold, 1.15-fold), and downregulates Sur-1 (0.69-fold, 0.37-fold). Immunofluorescence analysis indicated that 5 μM melittin downregulates Kir6.2 and Sur-1 while upregulates Sur-2 subunits in small DRG neurons where these channels are abundent.

Conclusions: In conclusion, melittin distinctly regulates the Sur-1 coupled Kir6.2 compared to Sur-2 coupled Kir6.2, and further pharmacological analysis could explain their contribution to peripheral pain mechanisms associated to nerve injury.

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P248

IBA-1 SILENCING INTERFERES WITH P2X7 FUNCTIONING IN BV2 MICROGLIA

Melania-Maria Bica-Popi[1], Roxana-Olimpia Gheorghe[1], Alexandru-Florian Deftu[1,2], Violeta Ristoiu[1]

1Department of Anatomy, Animal Physiology and Biophysics, Faculty of Biology, University of Bucharest, Romania. 2The research Institute of the University of Bucharest(ICUB), Romania

melaniabicapopi@yahoo.com

Aims: The microglial actin-binding cytoskeletal protein Iba-1 is involved in membrane ruffling during phagocytosis via calcium binding path. Calcium is believed to be a major signal transducer modulating the actin cytoskeleton. When activated by BzATP, P2X7 become a high-conductance channel permeable not only for calcium ions, but for large molecules as YO-PRO. Given the strong correlations between P2X7 and the cytoskeleton, we investigated if Iba-1 silencing could interfere with P2X7 functioning.

Methods: BV2 cells transiently transfected with scramble ARN (siRNA-01955) and silencing ARN (siRNA-18491) were maintaned 72h in culture until recording. Dorsal root ganglia macrophages from rats +/- treated with anti-Iba-1 siRNA after a Spinal Nerve Ligation lesion were extracted using MACS and were maintained in culture 8-10 hours until recording. The response to acute application of 300 µM BzATP for 20 seconds was measured using ratiometric microfluorimetry with Fura-2 fluorescent dye and analyzed with Imaging Workbench 4.0.

Results: The results in BV2 cells showed a significant increase of the calcium influx after Iba-1 silencing (1.041 ± 0.053, N=194) in comparison with the control condition (0.8545 ± 0.031, N=270, $P < 0.05$). In macrophages isolated from the DRG the effect on P2x7 receptors was as obvious.

Conclusions: Iba-1 silencing has different consequences on P2X7 functioning, depending of the type of cells. Additional experiments are required to explain this specificity.

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KIR2.1 CHANNELS CONTRIBUTE TO DIFFERENT MICROGLIA CELLS FUNCTIONS

Florian Armășescu[1], Bianca Brănescu[1], Violeta Ristoiu[1], Alexandru Deftu[1,2]

1Department of Anatomy, Animal Physiology and Biophysics, Faculty of Biology, University of Bucharest, Romania. 2TheRresearch Institute of the University of Bucharest (ICUB), Bucharest, Romania

florianarmasescu@gmail.com

Aims: The activity of microglial cells is influenced by many types of ion channels, including the inward-rectifier Kir2.1 potassium channels responsible also for the regulation of the resting membrane potential. While the activity of this ion channel can alter different functions in microglial cells, there are no studies indicating the contribution of Kir2.1 to microglial migration. In this study we investigated the expression of Kir2.1 in BV2 cells and their possible implication in cellular migration.

Methods: Whole-cell patch-clamp recordings were made on BV2 cells after 24 h in culture. ML-133 for Kir2.1 was used as a specific inhibitor. The scratch assay test was used to quantify microglial migration after 24 h in culture.

Results: ML-133 inhibited the currents at + 40 mV, from 150.615 pA in control conditions to 49.542 pA after the treatment, and at -120 mV from -278.392 pA to -192.251 pA. The results confirmed the presence of Kir2.1 ion channels in BV2 cells. In addition, scratch assay tests indicated that 20 μM of ML-133 can alter the migration of BV2 cells after 24h in culture.

Conclusion: BV2 microglia express Kir2.1 ion channels which contribute to the migration process. Further experiments are needed to highlight the link between Kir channels and cellular migration.

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THE IMPACT OF OXYTOCIN ON MATURE HIPPOCAMPAL NEURONS' VULNERABILITY TO IN VITRO METABOLIC DEPRIVATION DEPENDS ON THE SEVERITY OF LESION

Robert Mihai Haret[1], Ioana Florentina Grigoras[1], Mara Ioana Iesanu[1], Diana Maria Chitimus[1], Rosana-Bristena Ionescu[1], Bogdan Ianosi[2], Mihai Ceanga[3], Ana-Maria Zagrean[1]

1Discipline of Physiology and Neuroscience, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania. 2Neurological Intensive Care Unit, Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria. 3Hans Berger Department of Neurology, Jena University Hospital, Jena, Germany.

robert.haret@stud.umfcd.ro

In vitro oxygen-glucose deprivation (OGD) mimics cerebral ischemia, leading to ionic homeostasis alterations. Oxytocin was shown to upregulate the chloride cotransporter KCC2 and to play a role in the excitation-inhibition balance, exerting a neuroprotective effect on immature hippocampal cultures subjected to OGD-reoxygenation.

Here we investigate the oxytocin treatment effect on mature neuronal cultures subjected to OGD.

Primary hippocampal cultures were obtained from postnatal day 0 Wistar rat pups. At 7 days in vitro, cell cultures were subjected to either OGD episodes of 2h or control (normoxic-normoglycemic) conditions. Both the OGD and the control group received treatment with 0.1µM or 1µM oxytocin. Cellular viability was measured by means of a metabolic assessment using resazurin during 3h of reoxygenation in a normoglycemic medium. Significance was calculated using ordinary two-way ANOVA and post-analysis Tukey's multiple comparisons test. A p-value <0.05 was considered statistically significant.

OGD decreased cellular viability to 50%-70% of control, considered as moderate lesion, or to <50%, considered as severe lesion. Neither 0.1µM, nor 1µM oxytocin treatment did significantly affect the viability of mature hippocampal cultures having suffered a moderate lesion. However, after a severe lesion, both oxytocin concentrations caused a significant increase in cellular viability ($p<0.05$).

Our results suggest that oxytocin increases mature neuronal viability only after a severe hypoxic injury, which could sustain oxytocin neuroprotective effect in intracellular chloride high level conditions, like post-excitotoxicity or in immature brain. Further research is needed to understand the mechanisms through which oxytocin modulates intracellular chloride and influence excitability in different physio-pathologic conditions.

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P251

BDNF POTENTIATES SPONTANEOUS AND EVOKED ACETYLCHOLINE RELEASE IN MICE MOTOR SYNAPSES VIA MULTIPLE MECHANISMS

Alexander Gaydukov, Anastasia Molchanova, Ekaterina Tarasova, Olga Balezina

Moscow State University, Biology Dept., Moscow, Russia

gaydukov@gmail.com

Aims: Recently we have shown that stimulation of postsynaptic PAR1 thrombin receptors suggested the release of BDNF as a retrograde signal. The particular signaling pathways triggered by BDNF followed by changes in synaptic transmission in mouse motor synapses have been investigated poorly.

Methods: The mechanisms underlying the BDNF-induced modulation of acetylcholine release were studied using intracellular microelectrode recordings of miniature endplate potentials (MEPPs) and multiquantal endplate potentials (EPPs) in mouse diaphragm neuromuscular preparations.

Results: BDNF (1 nM) increased both the MEPP frequency and amplitude. Phospholipase C mediates the increase only in MEPP frequency. The increase in MEPP amplitude was due to the quantal size enhancement since this effect was prevented by vesamicol or bafilomycine A1. BDNF-induced increase in quantal size, but not in MEPP frequency was fully prevented by blocking MEK/Erk-pathway with U0126 or by inhibition of PKA with H-89. The activity of adenosine A2A-receptors is required for the manifestation of BDNF effect on MEPP amplitude: A2A-blocker ZM241385 greatly diminished the BDNF effect on MEPP amplitude. On the contrary, prolonged stimulation of A2A-receptors with CGS21680 increased the amplitude of MEPPs by itself and occluded the BDNF effect. BDNF increased EPP amplitude in short trains (50 Hz, 1 s) mainly due to the increase in the quantal size since the EPP quantal content was increased only at the beginning of EPP train.

Conclusion: Our data suggest that BDNF simultaneously triggers multiple presynaptic signaling pathways leading to upregulation of acetylcholine release in motor synapses.

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P252

COGNITIVE DECLINE AND PLASMA CYTOKINE PROFILE IN PATIENTS WITH SYNUCLEINOPATHIES WITH DEMENTIA

Usenko T.S.[1,2], Nikolaev M. A.[1,2], Bezroukova A.I.[1], Gracheva E.M.[1], Milukhina I.V.[3], Belceva Y.A.[4], Zalutskaya N.M.[4], Timofeeva A.A.[1], Pchelina S.N.[1,2,3]

1Petersburg Nuclear Physics Institute, Saint-Petersburg, Russia. 2First Pavlov State Medical University of St. Petersburg, Saint Petersburg, Russia; 3Institute of Experimental Medicine, Saint-Petersburg, Russia. 4V.M. Bekhterevs National Medical Research Center Psychiatry and Neurology, Saint Petersburg, Russia

tatiana.s.usenko@gmail.com

Introduction: Microglia activation plays a central role in the inflammatory response in chronic neurodegenerative diseases as dementia with Lewy body (DLB), Parkinson's disease (PD) (synucleinopathies) and could be mediated with accumulation of neurotoxic alpha-synuclein. Last data suggest that neuroinflammation may contribute to cognitive impairment.

Aim: Aim of the current study was to estimate relationship between plasma cytokine profile and cognitive status in patients with synucleinopathies with dementia.

Materials and methods: Plasma cytokine levels (IFN-gamma, IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-21, IL-23, IL-1b, TNFα, MCP-1) were detected in 16 patients with DLB, 20 patients with PD with dementia (PDD), 28 patients with PD without dementia (PD) by a Luminex array system with Milliplex MAP. Cognitive levels vere assessed with the Mini–Mental State Examination (MMSE).

Results: TNFα plasma levels were elevated in patients with synucleinopathies with dementia (DLB, PDD) than in PD patients ($p=0.025$, $p=0.033$, respectively). IFN-gamma and IL-6 plasma levels were increased in DLB patients compared to PD patients ($p=0.037$, $p=0.033$, respectively). Multiple linear regression analysis performed the relationship between MMSE score of patients with dementia (DLB,PDD) and IL-2, IL-10, IL-1β, IL-21, IL-23 and IFN-gamma plasma levels ($p<0.0001$, $F=14.07$, $R2=0.77$).

Conclusion: This is the first study estimating plasma cytokines profile in DLB patients. Our study demonstrated that the development of dementia in synucleinopathies is associated with an elevated plasma proinflammatory cytokine levels.

This study was supported by RFBR grant N 18-315-00387 mol-a

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P253

EFFECT OF BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) ON BEHAVIOR AND BRAIN MONOAMINES IN MICE DIFFERED BY PRESYNAPTIC 5-HT1A RECEPTOR SENSITIVITY

Vladimir S. Naumenko, Elena M. Kondaurova, Daria V. Bazovkina, Ekaterina Yu. Bazhenova, Nina K. Popova

Federal Research Center Institute of Cytology and Genetics, Siberian Division of the Russian Academy of Science, Novosibirsk, Russia

naumenko2002@mail.ru

Presynaptically localized 5-HT_{1A} receptor is involved in the regulation of the brain serotonin (5-HT) system functioning and is seems to play an important role in the cross-talk between 5-HT and brain-derived neurotrophic factor (BDNF) systems as well as in the antidepressant drug action. Recently we have shown that mice of congenic B6.CBA-D13Mit76C (B6-M76C) mouse line created by transferring 105.89-118.83 Mbp fragment of chromosome 13 containing 5-HT_{1A} receptor gene from CBA mice to C57BL/6 genetic background demonstrate reduced sensitivity of presynaptic 5-HT_{1A} receptor compared to control B6.CBA-D13Mit76B (B6-M76B) mouse line.

We used these mice in order to investigate whether presynaptic 5-HT_{1A} receptor affect the response to acute BDNF treatment.

Central BDNF administration (300 ng i.c.v.) increased exploratory activity and aggressiveness in control B6-M76B mice. These behavioral changes were accompanied by reduction of 5-HT_{2A} receptor functional activity. Also BDNF increased brain 5-HT and its main metabolite 5-hydroxyindoleacetic acid (5-HIAA) levels in the midbrain. Furthermore, BDNF elevated the dopamine (DA) level in the midbrain as well as DA and its metabolites homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) levels in the striatum of control B6-M76B mice. In contrast, in B6-M76C mice BDNF reduced only 5-HT_{1A} receptor functional activity and increased DOPAC level in the midbrain.

The obtained data indicate that decreased presynaptic 5-HT_{1A} receptor sensitivity in B6-M76C mice is associated with lowered response to BDNF.

Animal maintenance was supported by basic research project # 0324-2019-0041. The study was supported by the RSF grant # 17-15-01021.

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P254

EFFECT OF CHRONIC ETHANOL TREATMENT ON BEHAVIOR AND EXPRESSION OF BRAIN-DERIVED NEUROTROPHIC FACTOR AND ITS RECEPTORS IN THE MOUSE BRAIN STRUCTURES

Bazovkina DV[1], Pershina AV[2], Il'chibaeva TV[1], Naumenko VS[1], Popova NK[1]

1Department of Behavioral Neurogenomics, Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences, Novosibirsk, Russia. 2Novosibirsk State University, Faculty of Natural Sciences, Novosibirsk, Russia

drinterf@ngs.ru

The Brain-derived neurotrophic factor (BDNF) plays significant role in brain functions. The precursor protein proBDNF can initiate apoptosis through p75 receptor, whereas binding of mature BDNF to TrkB receptor stimulates neurogenesis. Chronic alcoholization leads to neurodegeneration and behavioral dysfunction.

The aim was to evaluate the effect of chronic ethanol treatment on behavior and brain expression of BDNF and their p75 and TrkB receptors on adult C57Bl/6 mouse males.

Influence of prolonged ethanol exposure (10%, orally, 6 weeks) was estimated on 1) behavior in the open-field, forced swim and tail suspension tests, 2) levels of proBDNF and BDNF proteins and their p75 and TrkB receptors using Western-blotting and 3) expression of genes encoding these proteins in brain structures (hypothalamus, prefrontal cortex, hippocampus, amygdala, midbrain) using real-time PCR.

Chronic ethanol administration produced the increase in locomotor activity without any effects on depressive-like behavior. Alcoholization decreased mRNA level of Bdnf gene in midbrain ($p<0.05$) and increased proBDNF protein levels in midbrain ($p<0.05$) and prefrontal cortex ($p<0.05$) compared to control group. Also, the tendencies of ethanol effect were found: a decrease in mRNA level of gene encoding p75 receptor in cortex ($p=0.07$) and an increase in mRNA level of gene encoding BDNF in hypothalamus ($p=0.08$) and amygdale ($p=0.08$). No effects of alcoholization on the p75 and TrkB protein levels in all studied structures were detected.

Thus, chronic ethanol treatment alters the expression patterns of proBDNF protein and gene encoding BDNF in the mouse brain.

The work was supported by RNF, research project No.17-15-01021.

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P255

THIAMINE INDUCES SIRTUIN 5 IN CEREBRAL CORTEX OF RATS AFTER SPINAL CORD INJURY AND IMPROVES REHABILITATION

A.I.Boyko[1], P.M. Tsepkova[1], S.I. Ryabov[2], and V.I.Bunik[1,3]

1Faculty of Bioengineering and Bioinformatics, Lomonosov Moscow State University, Moscow, Russia. 2Russian Cardiology Research-and-Production Complex, Ministry of Health of the Russian Federation, Moscow, Russia. 3Belozersky Institute of Physico-Chemical Biology, Lomonosov Moscow State University, Moscow, Russia

boiko.sash@gmail.com

Aim: The brain is affected by severe spinal cord injuries (SCI). We studied the delayed effects of SCI on the acylation system in cerebral cortex, regarding producers of succinyl-CoA (2-oxoglutarate dehydrogenase complex, OGDHC), glutaryl-CoA (2-oxoadipate dehydrogenase complex, OADHC), their activator thiamine and desuccinylase/deglutarylase sirtuin 5 (Sirt5).

Methods: The SCI modelling, thiamine treatment and rehabilitation assessment by the Basso, Beattie, Bresnahan scale (BBBS) were as published (Boyko et al., 2018). Cerebral cortices for analysis were obtained 8 weeks post-SCI. Expression of Sirt5 and DHTKD1-encoded 2-oxoadipate dehydrogenase component of OADHC was estimated by immunoblotting. Assays of OGDHC and extramitochondrial OADHC were as described (Tsepkova et al., 2017).

Results: Compared to the cerebral cortices of sham-operated animals, those after SCI exhibited 2-fold changes in activities of OGDHC (inactivation, $p<0.001$) and extramitochondrial OADHC (activation, $p=0.07$) Rehabilitation of the self-healing animals possessing impaired OGDHC improved with elevated glutaryl-CoA producer ($r=0.6$, $p=0.04$ for BBBS vs DHTKD1 protein) and decreased deglutarylase expression ($r= -0.5$, $p=0.1$ for BBBS vs Sirt5). Compared to the self-healing animals, the rats with thiamine administration after SCI improved locomotor recovery by 25% ($p=0.002$), increasing Sirt5 level 3.5-fold ($p<0.0001$) and OGDHC activity 1.7-fold ($p=0.14$). Simultaneously, activity of extramitochondrial OADHC decreased 2-fold ($p=0.25$). Thus, when thiamine is administered after SCI, the recovery improves at increased Sirt5 and normalized production of succinyl- and glutaryl-CoAs.

Conclusion: Delayed effects of SCI on the rat cerebral cortex involve reciprocal changes in the producers of succinyl- and glutaryl-CoAs. Thiamine administration after SCI normalizes these changes, induces Sirt5, and improves rehabilitation.

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IMPLICATION OF NIGROSTRIATAL DOPAMINE SYSTEM IN THE REGULATION OF GENETICALLY-DEFINED AGGRESSIVE BEHAVIOR IN RATS

A.S. Tsybko[1], T.V. Ilchibaeva[1], R.V. Kozhemyakina[2], D.V., Eremin[1,3], V.S. Naumenko[1]

1Department of Behavioral Neurogenomics. 2Laboratory of Evolutionary Genetics, The Federal Research Center Institute of Cytology and Genetics SB RAS, Novosibirsk, Russia. 3Novosibirsk State University, Novosibirsk, Russia

antoncybko@mail.ru

Aims: The expression of the key genes of dopaminergic (DA) system in the substantia nigra (SN) and striatum (St) as well as behavioral responses on activation of D2 receptors in Norway rats selectively bred for high level of aggression towards man or its absence were investigated.

Methods: Expression of tyrosine hydroxylase (TH), DA transporter (DAT), D1 and D2 receptors and catechol-O-methyltransferase (COMT) was assessed by real time RT-PCR and western-blot analysis. DA turnover was studied by HPLC. Behavior effects of D2 receptor activation by highly selective agonist sumanirole were studied in the handling test and test for intermale aggression.

Results: Significant decrease in TH, DAT and D2 mRNA levels was found in the SN and simultaneously a significant increase in COMT and D2 genes expression was found in the St of highly aggressive rats. The protein level of the D1, D2, DAT as well as COMT was increased in the St of aggressive animals. However, we have not found any changes in DA metabolism. Sumanirole (2.5 mg/kg, i.p. acutely) effectively reduced the severity of defensive aggression and increased the number, latent and total time of social interactions in aggressive rats

Conclusion: Considerable differences in expression of the key DA genes in the nigrostriatal system between highly aggressive and tame rats were shown for the first time. The data suggested the implication of DA system in the mechanism of aggressiveness and in the development of either aggressive or nonaggressive phenotype as well.

The work supported by the RFBR (#17-04-00183).

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ДНС SNS Друштво за неуронауке Србије Serbian Neuroscience Society
National Neuroscience Society of Romania
Neuroscience Society of Turkey

Thursday, July 11, 2019

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POSTER SESSION 2

P257

TIME-COURSE TRANSCRIPTOME ANALYSIS REVEALS LONG-TERM EFFECTS OF LACTATE ON GENE EXPRESSION AND NOVEL SIGNALING PATHWAYS MODULATED IN CORTICAL NEURONS

Michael B. Margineanu, Hubert Fiumelli, Pierre J. Magistretti

[1]Laboratory for Cellular Imaging and Energetics, Biological and Environmental Sciences and Engineering Division (BESE), King Abdullah University of Science and Technology (KAUST), Thuwal, Saudi Arabia

michael.margineanu@kaust.edu.sa

Aim and Methods: Lactate potentiates NMDA receptor activity and regulates genes important for synaptic plasticity and neuroprotection, modulates the excitability of neurons, and plays an important role in learning and memory. Here we describe a time course genome-wide transcriptome study that unravels novel genes regulated by lactate in cortical neurons.

Results: Differential gene expression (DGE) analysis identified 5009 genes modulated by lactate after treatment for 1h, 6h, and 24h, out of 14264 expressed genes in the neuronal culture. Functional downstream bioinformatics analysis identified nine gene ontology pathways modulated by lactate in a time-dependent manner including MAPK signaling, circadian rhythm, amphetamine, cocaine and morphine addiction, retrograde endocannabinoid signaling, focal adhesion, gap junction, and glutamatergic synapse. Transcription factors with enriched binding motifs in the promoter of differentially expressed genes after 1h and 6h were CREB1 and respectively Egr1, Klf4, SP1, and MZF1. A time course-specific DGE analysis identified 289 genes with statistically significant temporal expression profile changes that were grouped in 6 clusters based on the time-dependent pattern of regulation. Cluster-specific gene ontology analysis identified common biological functions for these genes in cognition and regulation of phosphorylation, among others. The modulatory effect of lactate on a subset of activity-dependent, neuroprotection and synaptic plasticity genes was reduced in presence of AR-C155858, an inhibitor of monocarboxylate transporters, suggesting that uptake of lactate into neurons is necessary for modulating gene expression.

Conclusions: Overall, these results provide further insights into the molecular mechanisms of lactate signaling in the brain and identify novel target genes and upstream regulators involved.

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WHOLE EXOME SEQUENCING IMPLICATES GRIN3A AND NOTCH4 IN PARKINSON'S DISEASE

Bashayer Al-Mubarak[1,2], Eman Al Yemni[1,2], Nada Al-Tassan[1,2]

1Behavioral Genetics Unit, Department of Genetics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. 2Saudi Human Genome Program, King Abdulaziz City for Science and Technology, Riyadh, Saudi Arabia.

bal-mubarak@kfshrc.edu.sa

A variety of genetic approaches have been employed to elucidate the genetic basis of Parkinson's disease (PD), yet, no universal risk variant(s) have been found. At least 40 different loci have been implicated from genome-wide association studies and an equal number of candidate genes have been revealed by whole exome sequencing (WES). Thus, highlighting the genetic heterogeneity of PD. However, the majority of WES findings in PD are derived from familial cases, while the more common (sporadic from) remains under-investigated.

Aim: In this study, we devised a 3-stage analysis strategy suited for the discovery of rare potentially deleterious variants in complex disorders.

Methods: Combined molecular analysis involving screening of copy number and single nucleotide changes using WES and MLPA approaches.

Results and conclusion: We successfully identified 125 variants within 117 genes in 51/60 cases. From which a shortlist of prioritized variants that are more likely to contribute to the disease was curated. Moreover, all the genes revealed here have not been previously described in PD apart from (EIF4G1 and ATP13A2). Among our prioritized genes, GRIN3A and NOTCH4 stood out as the strongest candidates. NOTCH4 participates in NOTCH signaling pathway essential for angiogenesis which if disrupted can lead to neurodegeneration. On the other hand, GRIN3A, encoding NMDA receptor subunit GluN3A, is a key player in controlling excitatory NMDAR activity. Abnormal glutamate transmission via NMDAR has been implicated in the development of levodopa-induced dyskinesia in PD patients. Finally, our comprehensive approach uncovered a list of candidate variants warranting functional assessment.

P259

DOES PROBENECID IMPAIR ASTROCYTE MIGRATORY CAPACITY VIA COMPETITIVE INHIBITION OF P2X7 RECEPTOR OR BY BLOCKING PANNEXIN 1 CHANNEL?

MarijaAdzic[1,2], Nadezda Nedeljkovic[1]

1Institute for Physiology and Biochemistry, Faculty of Biology, University of Belgrade, Belgrade, Serbia;
2The Centre for Laser Microscopy, Faculty of Biology, University of Belgrade, Belgrade, Serbia

adzic_marija@yahoo.com

Aim: Purinergic P2X7 receptor is a trimeric low-affinity ligand-gated channel activated upon extracellular adenosine 5'-triphosphate (ATP) binding. In the presence of high ATP concentrations P2X7 forms a large pore that allows passage of larger organic cations. It has been previously shown that probenecid (p-(di-n-propylsulfamyl)-benzoic acid; Benemid® or Benuryl®), which inhibits Pannexin1 channel-mediated transport of organic anions, also competitively blocks P2X7 pore formation. The aim of this study is to elaborate weather the inhibitory effect of probenecid on astrocyte migration in vitro, is mediated via P2X7 or Pannexin1 channel interference.

Methods: Astrocyte migratory capacity has been analyzed using a scratch wound (SW) assay in primary rat cortical astrocyte monolayer. Data obtained over the time after the scratching (0-24 h) provided quantitative data showing wound area closure and cell front displacement velocity. Migratory capacity of astrocytes was analyzed in the cultures treated either with probenecid or A438079, which is selective P2X7 receptor inhibitor and the data were compared with control untreated astrocyte cultures. Extracellular adenosine production by the ecto-5'-nucleotidase/CD73 was analyzed as well, since the nucleoside affects astrocyte migration in vitro.

Results: Data showed significant slowdown of wound healing in probenecid-treated astrocyte cultures, with significantly reduced area coverage and cell front displacement velocity in comparison to control cultures after 24 h. In cultures treated with P2X7 receptor blocker, astrocyte migration was not significantly affected. The production of adenosine was not elevated under both treatments compared to the control.

Conclusions: Probenecid affects rat astrocyte migration mostly by blocking Pannexin1, but its effect contribution via P2X7 is yet to be analyzed.

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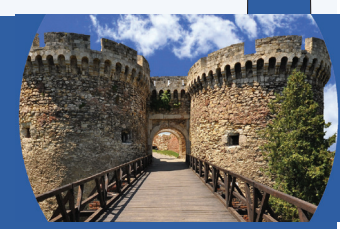

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TREATMENT WITH VITAMIN B COMPLEX IMPROVES RECOVERY OF INJURED PERIPHERAL MOTOR NERVE BY ENHANCING SCHWANN CELLS MATURATION AND MACROPHAGE POLARIZATION TOWARDS M2 PHENOTYPE

Biljana Bozic Nedeljkovic[1,2], Adil Ehmedah[1], Predrag Nedeljkovic[3], Sanja Dacic[1], Biljana Draskovic Pavlovic[2], Dragana Vucevic[2], Sanja Pekovic[4]

1Institute of Physiology and Biochemistry "Ivan Djaja", Faculty of Biology, University of Belgrade, Belgrade, Serbia. 2Institute for Medical Research, Faculty of Medicine, Military Medical Academy, University of Defense in Belgrade, Belgrade, Serbia. 3Institute for Orthopedic Surgery "Banjica", Belgrade, Serbia. 4Department of Neurobiology, Institute for Biological Research "Sinisa Stankovic", University of Belgrade, Belgrade, Serbia.

biljana@bio.bg.ac.rs

Locomotor impairments following peripheral nerve injury (PNI) in humans can be particularly devastating and significantly impede quality of life due to restricted recovery. With an aim to improve recovery after the PNI we tested effects of vitamin B (B1, B2, B3, B5, B6, B12) complex therapy on overall nerve repair. Given that macrophages play a core role in this, we focused primarily on macrophage-mediated repair in PNI setting, and the macrophage-mediated migration and proliferation of Schwann cells, which has important implications in PNIs.

Adult male Albino Oxford rats were used. Surgery: Motor branch of femoral nerve was transected and immediately reconstructed by end-to-end anastomosis. Experimental groups: (O) operated animals, (OT) operated and daily treated with vitamin B complex for 14 days in following doses (mg/kg/day): B1-37; B2-3.7; B3-93; B5-9.3; B6-7.4; and B12-3.7μg/kg/day. (S) sham-operated animals, underwent the same procedure but without transection of nerve. Pre- and post-operatively behaviour tests were performed. Animals were sacrificed 1, 3, 7, and 14 days post-injury. Isolated nerves were used for immunofluorescence analysis.

Two-week treatment with vitamin B complex applied after the PNI supported recovery of walking function, promoted remyelination due to enhanced Schwann cells proliferation, maturation and differentiation, and shifts macrophage polarization towards M2 phenotype, considered to play reparative roles.

Our data suggest that vitamin B complex therapy, by regulating macrophages polarization and macrophages-Schwann cells interplay, may have the potential to improve regenerative outcomes in PNI, and we believe that such an approach holds potential for patients who suffer from chronic disability following PNI.

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WHAT HAPPENS AFTER APPLICATION OF THIAMINE IN THE BRAIN OF JAPANESE QUAILS TREATED WITH CHLORPYRIFOS

Dejana Ćupić Miladinović[1], Sanja Peković[2], Sanja Dacić[3], Isidora Filipović[4], Maja Životić[4], Milena Đorđević[5], Miloš Blagojević[5], Ivana Nešić[5], Sunčica Borozan[6]

1Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine, University of Belgrade, Belgrade, Serbia. 2Department of Neurobiology, Institute for Biological Research "Sinisa Stankovic", University of Belgrade, Belgrade, Serbia. 3Department for Physiology and Biochemistry, Faculty of Biology, University of Belgrade, Belgrade, Serbia. 4Institute of Patology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia. 5Department of Anatomy, Faculty of Veterinary Medicine, University of Belgrade, Belgrade, Serbia. 6Department of Chemistry, Faculty of Veterinary Medicine, University of Belgrade, Belgrade, Serbia.

dexyc.vet@gmail.com

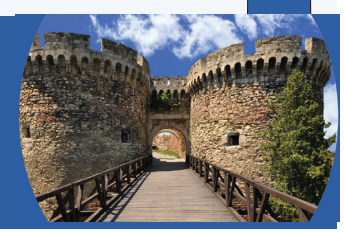
By following the pathohystologycal changes in the hippocampus, cerebellum, cerebral cortex of Japanese quail (Coturnix japanica) treated with chlorpyrifos we aimed to investigate the influence of vitamin B1 (thiamine). Antioxidative activity of thiamine was assessed by monitoring the nitrite concentration(NO_2^-), and activities of glutathione(GSH) and glutathione S-transferase(GST), as agents of cellular detoxification.

Study was conducted on forty male quails (2 controls and 2 experimental groups, n= 10), 3-4 weeks old. First control group was treated only with vitamin B1, while second one received pure corn oil. CPF dissolved in corn oil was administered by gavage, at dose of 3 mg/kg BW while another group recived 10 mg/kg BW of vitamin B1 i.m. 30 min after CPF administration for 7 consecutive days.

CPF has led to increase, while thiamine treatment coused a decrease in NO2- concentration. CPF induced changes in GSH and GST levels, while group treated with vitamin B1 showed significant ($p < 0.0001$) increase of these parameteres, proving important role of thiamine in the detoxification and elimination of pesticides.

In hippocampus group that received CPF showed signs of edema with numerous damaged neurons, especially in pyramidal layer, while in group that received vitamin B1, changes were similar, but less prominent. In cerebellum group that received CPF showed large number of degenerated Purkinje cells, while with vitamin B1 the reduction of degenerated neurons is present. Cerebral cortex showed degeneration with pycnotic nuclei of many neurons, edema and congestion in groups which received CPF and also similar changes were found after application of B1.

These results confirm that CPF causes oxidative stress and degenerative changes, while supporting the hypothesis of thiamine as "antistress vitamin".



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L-TYPE CALCIUM CHANNELS INVOLVEMENT IN THE REGULATION OF NEUROINFLAMMATION AND NEUROREGENERATION AFTER BRAIN INJURY

Sanja Dacic[1], Iva Bozic[2], Rada Jeremic[3], Ivana Bjelobaba[2], Irena Lavrnja[2], Danijela Savic[2], Ljubisav Rakic[4], Mirjana Stojiljkovic[2], Sanja Pekovic[2]

1Institute of Physiology and Biochemistry "Ivan Djaja", Faculty of Biology, University of Belgrade, Belgrade, Serbia. 2Department of Neurobiology, Institute for Biological Research "Sinisa Stankovic", University of Belgrade, Belgrade, Serbia. 3Institute of Medical Physiology "Richard Burian", Faculty of Medicine, University of Belgrade, Belgrade, Serbia. 4Serbian Academy of Sciences and Arts, Belgrade, Serbia.

sanjas@bio.bg.ac.rs

Aims: Traumatic brain injury (TBI) causes disruption in homeostasis of calcium ions (Ca2+), important second messenger considered as the major culprit of secondary injury and TBI-induced neuronal damage and death. Ca2+ entry into the cells occurs via various types of voltage-dependent calcium channels (VDCCs). The aim of this study was to evaluate the involvement of Ca2+ entry via L-type CaV1.2 VDCCs in the processes of neuroinflammation and regeneration after brain injury.

Methods: TBI was performed on male Wistar rats by sensorimotor cortex ablation (SCA) at the following coordinates: 2 mm anterior and 4 mm posterior to bregma, and 4 mm lateral from the midline. Temporal and cellular pattern of CaV1.2 expression was followed at different time points post-injury (2, 7, 14, 30 dpi) using double immunofluorescence staining with specific markers.

Results: Upregulation of CaV1.2 expression was detected on reactive astrocytes and astrocytic processes that form glial scar around the lesion site, on subset of proinflammatory microglia/macrophages and neutrophils surrounding the lesion cavity. Interestingly, presence of CaV1.2+ cells was detected in the migratory pathway, consisted of DCX+ progenitors, extending from subventricular zone up to the lesion site. Furthermore, CaV1.2+/DCX+ newborn neurons were detected in subgranular layer of hippocampal dentate gyrus.

Conclusions: We concluded that L-type CaV1.2 calcium channel has an important role in the regulation of processes of neuroinflammation, neuroregeneration and neurogenesis, pointing to the complexity of intercellular regulation of Ca2+ homeostasis after brain injury. Consequently, modulation of CaV1.2 channels expression may be potential target for the treatment of brain injury.

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MOLECULAR MECHANISMS OF ETHYL PYRUVATE TOLEROGENIC EFFECTS ON DENDRITIC CELLS

Neda Đedović[1]*, Đorđe Miljković[1], Irena Lavrnja[2]

1Department of Immunology, Institute for Biological Research "Siniša Stanković", University of Belgrade, Belgrade, Serbia. 2Department of Neurobiology, Institute for Biological Research "Siniša Stanković", University of Belgrade, Belgrade, Serbia

ndjedovic@yahoo.com

Aims: Tolerogenic dendritic cells (tolDC) have immuno-regulatory properties and they are a promising prospective therapy for multiple sclerosis, as well as for other autoimmune diseases. Ethyl pyruvate (EP) is a redox analogue of dimethyl fumarate (Tecfidera), a drug for multiple sclerosis treatment. We have recently shown that EP has the ability to direct DC towards tolDC in both murine and human DC. Therefore, we expanded our investigation to determine which mechanisms are responsible for EP-imposed tolerance in DC. Therefore, we examined Nrf2 signalling pathway, HO-1 and NQO1 enzymes, and NF-κB transcription factor.

Methods: C57BL/6 mice bone marrow derived DC were cultivated for 8 days in the presence of 20 ng/mL of GM-CSF without (immature DC - iDC) or with EP added on days 3 and 6 (EP-DC). In order to induce maturation, iDC and EP-DC were incubated for 15min - 4 h with 100 ng/mL lipopolysaccharide (mature - mDC and tEP-DC, respectively). After that, immunocitochemistry staining was performed.

Results: Maturation of DC led to reduction of the Nrf2 and HO-1 expression, yet this reduction was prevented by EP. Also, the NQO1 expression was higher in EP-DC in comparison to iDC. However, the expression in tEP-DC was lower than in mDC, but still higher than in iDC. Finaly, unlike mDC had higher levels of nuclear NF-κB than iDC, tEP-DC had lower expression compared to EP-DC.

Conclusions: EP exercises its tolerogenic potential on DC through the up-regulation of anti-oxidative signaling pathways, as well as through the inhibition of proinflammatory transcription factor NF-κB.

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P264

ANATOMICAL AND CELLULAR DISTRIBUTION OF ECTO-NUCLEOSIDE TRIPHOSPHATE DIPHOSPHOHYDROLASE 2 IN RAT BRAIN

Milorad Dragić[1,2], Ivana Grković[2], Marija Adžić[1], Nataša Mitrović[2], Nadežda Nedeljković[1]

1Department for General Physiology and Biophysics, Faculty of Biology, University of Belgrade, Serbia. 2Department of Molecular Biology and Endocrinology, VINČA Institute of Nuclear Sciences, University of Belgrade, Serbia

milorad.dragic@bio.bg.ac.rs

Aims: Extracellular ATP and adenosine modulate various processes in the central nervous system, including neurotransmission, gliotransmission, synapse activity and blood flow. Their extracellular levels are tightly controlled by ectonucleotidase enzymes, which sequentially hydrolyze ATP to adenosine. NTPDase2 preferentially catalyzes ATP, with accumulation of ADP, and its regional and cellular distribution in CNS is largely unknown. Thus we aimed to investigate anatomical and cellular distribution of NTPDase 2 in CNS.

Methods: Three months old Wistar male rats were sacrificed and their brains were isolated and prepared for immunofluorescence staining

Results: Present immunohistochemical study shows somatic localization of NTPDase2 at neurons in the Purkinje cells, deep cerebellar nuclei, the brainstem nuclei, the caudoputamen and sensorimotor cortex and tectum of midbrain and in thalamus. Synaptic localization of NTPDase2 is observed in the caudoputamen and hippocampus. Also, NTPDase2 is localized at GFAP+ and VIM+ fibrous astrocytes in the white matter throughout the brain.

Conclusion: The regional and cellular pattern of NTPDase 2 expression suggests its dominant localization in the motor areas, underpinning possible role of the enzyme in motor functions.

This work was supported by the Ministry of Education, Science and Technological development, Republic of Serbia, grants No. 41014 and 173044.

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P265

LACK OF GLUN2A-CONTAINING NMDA RECEPTORS AMELIORATES SYNAPTIC PLASTICITY IN INFLAMMATION-INDUCED DEPRESSION: THE PROMINENT ROLE OF PSA-NCAM MOLECULE

Ester Francija[1], Zorica Petrović[1], Željka Brkić[1], Minja Milosavljević[1], Miloš Mitić[1], Emilija Glavonić[1], Jelena Radulović[2] and Miroslav Adžić[1]

1Department of Molecular Biology and Endocrinology, VINCA Institute of Nuclear Sciences, University of Belgrade, Serbia. 2Department of Psychiatry and Behavioural Sciences, The Asher Center of Study and Treatment of Depressive Disorders, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA

star@vin.bg.ac.rs

Aims: Data have demonstrated that N-methyl-D-aspartate receptor (NMDAR) is implicated in depression. In addition, deficient BDNF (brain-derived neurotrophic factor) signaling and reduced function of polysialylated form of the neural adhesion molecule (PSA-NCAM), molecules related to neuronal structural plasticity, in hippocampus may underlie the pathogenesis of depression. This study was undertaken to examine the role of GluN2A subunits of NMDAR on neuroplasticity markers (BDNF and PSA-NCAM) in LPS-induced model of depression, as well as to reveal how pharmacological inactivation of BDNF/TrkB signaling (tropomyosin-related kinase B) influences biochemistry and behaviour of LPS treated GluN2A knockout mice.

Methods: LPS was administered intraperitoneally to male C57Bl/6J wild-type and GluN2A knockout mice. TrkB antagonist, ANA-12, was administered intraperitoneally to knockout mice 23h after LPS treatment. 24 h after LPS, depressive-like behaviour was assessed by sucrose preference test (SPT). Levels of BDNF, PSA-NCAM and phospho-TrkB (p-TrkB) in hippocampal synaptosomes were also examined.

Results: LPS decreased sucrose preference, indicating depressive-like behaviour in wild-type but not in GluN2A knockout mice. Depressive phenotype of wild-type mice was linked to decreased levels of PSA-NCAM and BDNF. Oppositely, in GluN2A knockout mice levels of BDNF were increased, while PSA-NCAM levels were not altered by LPS. Surprisingly, systemic administration of ANA-12 to LPS treated knockouts increased PSA-NCAM levels and decreased BDNF-TrkB signaling but has no effect on depressive-like behavior measured by SPT.

Conclusions: These results indicate that GluN2A subunit is critical in neuroinflammation-related depression and it appears that resilience of GluN2A knockouts to inflammation-induced depression is more dependent on PSA-NCAM levels than the activity of BDNF-TrkB signaling.

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UP-REGULATION OF ECTO-5' NUCLEOTIDASE ON ACTIVATED MICROGLIAL CELLS FOLLOWING TRIMETHYLTIN-INDUCED NEUROTOXICITY OF FEMALE RATS

Ivana Grković[1], Milorad Dragić,[1,2], Nataša Mitrović[1], Marina Zarić[1], Dunja Drakulić[1], Nadežda Nedeljković[2]

1Department of Molecular Biology and Endocrinology, VINČA Institute of Nuclear Sceinces, University of Belgrade, Belgrade, Serbia. 2Department for General Physiology and Biophysics, Faculty of Biology, University of Belgrade, Belgrade, Serbia

istanojevic@vin.bg.ac.rs

Aims: Ecto-5'-nucleotidase (CD73) is an immunosuppressive molecule intricately involved in immune responses and is able to dephosphorylate AMP to adenosine. Activation of resident microglia is one of components in the progression of trimethyltin (TMT)-induced neurodegeneration. We hypothesized that CD73 could act as a switch for the morphological transition of microglia.

Methods: Three week after bilaterally ovariectomy, Wistar rats were treated with a single dose of TMT (8 mg/kg, i.p.) and sacrificed 2-, 4- and 7-days post-treatment. A combination of molecular and histological methods was used to determine activity and expression of CD73 in the hippocampus of TMT treated animals.

Results: Expression analysis of CD73 revealed biphasic response to TMT-intoxication: decrease at 2-d was followed by gradual increase 7-d post-TMT. Similar was shown by AMPase histochemistry and CD73- ir: after reduction of staining in synaptic regions 2-d post-treatment, increase of specific labeled glial cells that infiltrated neuronal layers from 4- to 7-d was observed. Activation of microglia during investigated timeframe was reflected as a huge increase in the cell number and the full repertoire of microglial shapes and forms, including unusual bushy and long, rod-shaped microglia. Four days post-treatment microglia changed morphology from resting to bushy/amoeboid type as a result of TMT-induced neurodegeneration. From that time-point CD73 nicely depicted processes of bushy microglia, while amoeboid type completely colocalized with CD73. At 7-d TMT, a specific rod microglia was completely delineated with CD73.

Conclusions: Degree of CD73 up-regulation correlates with morphologically distinct microglial phenotypes, suggesting the specific role of CD73 during microglia activation.

Supported by the Ministry of Education, Science and Technological development, Republic of Serbia, Grants III41014 and OI173044.

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P267

NTPDASE1/CD39 EXPRESSION INCREASED DURING EAE IN ASSOCIATION WITH NUMBER AND ACTIVATION STATE OF MICROGLIA/MACROPHAGES

Jakovljevic M[1], Lavrnja I[1], Bozic I[1], Milosevic A[1], Bjelobaba I[1], Savic D[1], Pekovic S[1], Nedeljkovic N[2], Laketa D.[2]

1Department of Neurobiology, Institute for Biological Research "Siniša Stankovic´ ", University of Belgrade, Belgrade, Serbia. 2Department for General Physiology and Biophysics, Faculty of Biology, University of Belgrade, Belgrade, Serbia

marija.jovanovic@ibiss.bg.ac.rs

Considering neuroinflammatory paradigm, increased extracellular levels of ATP have adverse effects, while adenosine is predominantly anti-inflammatory. In the CNS, NTPDase1/CD39 is the main enzyme that initiates the degradation pathway of extracellular ATP to adenosine.

The aim of the study was to explore the activation state of the cells that express NTPDase1/CD39 – microglia and macrophages, during experimental autoimmune encephalomyelitis (EAE).

Acute monophasic EAE was induced in female Dark Agouti rats. Animals were sacrificed at the disease onset (Eo), peak (Ep) and end (Ee). The lumbosacral parts of spinal cords were isolated for gene (qRT-PCR and in situ hybridization) and protein expression analysis (Western Blot, immunofluorescence and flow cytometry). Activation state of microglia/macrophages was assessed by colocalization analysis of NTPDase1/Iba1 and NTPDase1/CD68 with iNOS or Arg1 as specific markers of pro- and antiinflammatory state, respectively.

During EAE, NTPDase1/CD39 was significantly increased both at mRNA and protein level at Ep. Immunofluorescence combined with flow cytometry showed that reactive microglia and mononuclear infiltrates accounted for the most of the observed increase. Both Iba1 and CD68 microglia/macrophage markers showed higher co-occurrence with iNOS at Eo and Arg1 at Ep, suggesting prevalence of M1-like at Eo and M2-like at Ep. In addition, NTPDase1 showed about three-times higher colocalization with Arg1 compared to iNOS at Ep, suggesting its higher association with M2-like activation state of microglia/macrophages.

Together, our data suggest an association between NTPDase1 up-regulation by reactive microglia and infiltrated macrophages and their transition toward anti-inflammatory phenotype in EAE.

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P268

THE PROTECTIVE ROLE OF AMPK AND AUTOPHAGY IN NEUROTOXICITY CAUSED BY EXTRACELLULAR ALPHA-SYNUCLEIN

Marija Jeremić[1], Maja Jovanović[1], Marija Dulović[1], Gordana Tovilović Kovačević[2], Nevena Zogović[3], Ljubica Harhaji Trajković[3], Milica Vukojevic[1], Vladimir Kostic[4], Ivanka Marković[1]*, Vladimir Trajković[5]

1Institute of Medical and Clinical Biochemistry, School of Medicine, University of Belgrade, Belgrade, Serbia;
2Department of Biochemistry, Institute for Biological Research "Sinisa Stankovic", University of Belgrade, Belgrade, Serbia;
3Department of Neurophysiology, Institute for Biological Research "Sinisa Stankovic", University of Belgrade, Belgrade, Serbia;
4Clinic for Neurology, Clinical Center of Serbia, Biochemistry, School of Medicine, University of Belgrade, Belgrade, Serbia;
5Institute of Microbiology and Immunology, School of Medicine, University of Belgrade, Belgrade, Serbia

marijaj26@yahoo.com

Alpha-synuclein (ASYN) is regarded as one of the key culprits in pathogenesis of synucleinopathies, including Parkinson's disease, and impaired regulation of autophagy is associated with the ASYN aggregation. Autophagy is regulated by complex mechanisms, including AMP activated protein kinase (AMPK), a key energy sensor regulating cellular metabolism to maintain energy homeostasis. The aim of our study was to investigate the role of AMPK and autophagy in neurotoxic effect of secreted ASYN, as well as dopamine-modified and nitrated recombinant wild-type ASYN oligomers, on retinoic acid (RA)-differentiated SH-SY5Y cells.

The culture supernatant from neuroblastoma cells stably expressing wt ASYN was collected and used as conditioned medium (CM). The presence of wt ASYN in CM was confirmed by immunoblot, following lyophilisation.

The CM, as well as recombinant dopamine-modified or nitrated ASYN, all reduced viability in differentiated SH-SY5Y cells. This decrease in viability was accompanied by reduced AMPK activation, increased conversion of LC3-I to LC3-II and increase in Beclin-1 level, as demonstrated by immunoblot. Pharmacological activators of AMPK and autophagy (metformin and AICAR) significantly increased the cells' viability in the presence of CM and modified ASYN forms. Pharmacological inhibitors of autophagy (chloroqine, bafilomycin A1 and ammonium-chloride), further reduced cell viability in the presence of extracellular ASYN. The shRNA-mediated LC3 downregulation, as well as the RNA interference-mediated knockdown of ATG7 gene, both important for autophagosome biogenesis/maturation, increased sensitivity of SH-SY5Y cells to the extracellular ASYN-induced toxicity.

These data demonstrate the protective role of AMPK and autophagy against the toxicity of extracellular ASYN, suggesting that their modulation may be a promising neuroprotective strategy in Parkinson's disease.

P269

FISH OIL TREATMENT IN ADULTHOOD ALTERS FATTY ACID COMPOSITION AND CHOLESTEROL-RELATED GENE EXPRESSION AFFECTING THE VISUAL CYCLE IN MOUSE RETINA AND RPE

Irena Jovanovic Macura[1], Ivana Djuricic[2], Marjana Brkic[3], Desanka Milanovic[1], Sladjana Sobajic[2], Selma Kanazir[1] and Sanja Ivkovic[1]

1Institute for Biological research "Sinisa Stankovic", University of Belgrade, Serbia. 2Farmacy Faculty, University of Belgrade, Belgrade, Serbia. 3Center for the Promotion of Science, Belgrade, Serbia

irena.macura@ibiss.bg.ac.rs

Aims: Age-related macular degeneration (AMD) is a progressive and degenerative disease of the retina and major cause of blindness among the elderly population, whose etiology is not known. Changes in cholesterol metabolism and in the uptake of unsaturated fatty acids (DHA) in the retina and retinal pigmented epithelium (RPE) have been implicated in the pathogenesis of AMD. Because the continuous renewal of retinal membranes requires a constant supply of omega-3 fatty acids by RPE cells, diets rich in DHA may improve retinal function and may delay the development of exudative AMD. Thus, we hypothesized that short-term DHA supplementation (3 weeks), may serve as a prophylaxis in AMD prevention.

Methods: We used real-time PCR to quantify the expression pattern of genes regulating biosynthesis (hmgcr, lxrβ, srebp-2), transport (abca1, apoE) and elimination (cyp27, cyp46) of cholesterol and its metabolites and of two different DHA transporters - adipoR1 and mfsd2A, necessary for the photoreceptor proper function, in retina and RPE of control and FO treated animals (4 months-old). As a functional outcome we analyzed the expression profile of visual cycle genes in RPE.

Results: FO supplementation elicited significant changes in the phospholipid composition and transcriptional networks of the cholesterol-mediated and DHA transporter genes. Finally, FO supplementation decreased the expression of the key regulatory genes of the visual cycle in RPE.

Conclusions: As DHA requirements can vary across individuals according to genetic profile, it is important that the effects of DHA supplementation is carefully evaluated so that appropriate prophylactic recommendations can be made.

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P270

THE ROLE OF SOX2 AND SOX9 GENES IN REACTIVATION OF NT2-ASTROCYTES

Andrijana Klajn[1], Jelena Marjanović[1], Danijela Stanisavljević Ninković,[1] Vanda Balint[1], Jelena Popović[1], Marija Mojsin[1], Milena Milivojević[1], Vladanka Vuković[1], Milena Stevanović[1,2,3]

1Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Belgrade, Serbia. 2University of Belgrade, Faculty of Biology, Belgrade, Serbia. 3Serbian Academy of Sciences and Arts, Belgrade, Serbia

klajn.andrijana@gmail.com

Aims: Astrocytes provide mechanical, metabolic and trophic support to neurons. These cells have a unique ability to transform from quiescent into reactive state in response to injury in adult brain. However, the molecular mechanisms underlying functional properties of reactivated astrocytes are mostly unknown. The Sox family of transcription factors are well-known regulators of cell fate decisions during development. In response to injury, the astrocytes of adult brain reacquire properties of glia present in earlier developmental stages, including proliferation and migration competences. The aim of our study was to investigate protentional involvement of SOX2 and SOX9 in the reacquisition of proliferation and migration capabilities of quiescent astrocytes.

Methods: As a model system we used astrocytes deriving from pluripotent human embryonal carcinoma NT2/D1 cell line. We applied gain of function approach, using lentiviral vectors harboring human SOX2 and SOX9 genes. We compared the functional properties of SOX2 and SOX9-overexpressing NT2-astrocytes to empty-vectors transduced cells.

Results: Our results indicate that overexpression of SOX2 increases proliferation rate of mature NT2-astrocytes while SOX9 overexpression reactivates genes that performs key migratory roles during gliogenesis.

Conclusions: Proliferation and migration are basic cellular processes that underlies both gliogenesis and scar formation in adult brain. SOX genes have important roles in these processes in glial precursors and our results indicate they might control these processes also in reactivated astrocytes of adult brain. Targeting the functional properties of astrocytes may switch these cells to be potent endogenous defense mechanism that could be manipulated to promote neuronal survival and recovery.

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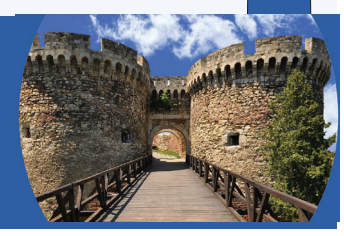

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THE EFFECT OF TIANEPTINE ON HIPPOCAMPAL CYTOSOLIC AND NON-SYNAPTIC MITOCHONDRIA SUB-PROTEOMES IN SOCIALLY ISOLATED RATS

Ivana Perić, Andrijana Stanisavljević, Dragana Filipović

Vinča Institute of Nuclear Sciences, University of Belgrade, Belgrade, Serbia

ivanap@vinca.rs

Aims: We investigated the effects of chronic social isolation (CSIS) in total duration of 6 weeks, a rodent model for studying depression, and/or chronic treatment with atypical antidepressant and anxiolytic Tianeptine (Tian) (3 weeks, 10 mg/kg/day),on cytosol and non-synaptic mitochondria (NSM) sub-proteomes in hippocampus of adult male Wistar rats. Our goal was to identify the most affected biological processes and activated pathways following CSIS and Tian treatment.

Methods: Behaviour testing for sucrose preference (SP), marble burying (MB) and forced swim test (FST), as indications of anhedonia, anxiety and behavioural despair, was performed. The purity of cell fractions was confirmed with Western blot. For comparative proteomic study we used HPLC-LTQ Orbitrap XL mass spectrometer and Sieve 2.0 software for relative quantification. STRING 11.5 was used for bioinformatic analysis.

Results: Tian normalized the CSIS-induced increase in SP and MB and decreased the immobility behaviour in FST. Bioinformatic analysis of proteomic data showed that Tian alone, increased the expression of proteasome system elements, redox system enzymes, enhanced energy metabolism and increased glyceraldehyde-3-phosphate dehydrogenase expression bound to NSM. CSIS led to an increase of antioxidative system proteins, increased proteasomal system proteins and down-regulated NSM proteins; while Tian-treatment of CSIS rats slightly suppressed the increase of proteasome elements and antioxidative enzymes, except for the increase of Cu-Zn superoxide dismutase, and increased the level of Lactate dehydrogenase.

Conclusion: Tian treatment indicates on possibly increased NSM metabolism and suppression of the CSIS-induced impairment of NSM functionality. Also, CSIS caused discrepancy in Tian effects in cytosolic fraction.

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P272

THE EFFECTS OF DIFFERENT DIETARY REGIMENS ON CHOLESTEROL METABOLISM IN THE CEREBELLUM OF AGING RATS

Milica Prvulović, Kosara Smiljanić, Smilja Todorović, Selma Kanazir, Aleksandra Mladenović Đorđević

Institute for Biological Research „Siniša Stanković", University of Belgrade, Belgrade, Serbia

milica.prvulovic@ibiss.bg.ac.rs

Aims: Dietary restriction (DR) has numerous beneficial effects on organism, starting from positive effect on life expectancy, to protective effects on cardiovascular system, blood lipid levels, immune response, glucoregulation, and neurological functions. Previously it has been shown that DR changes expression of genes and proteins involved in cholesterol metabolism, in both cerebral cortex and hippocampus. Herein we investigated cholesterol homeostasis in cerebellum, as a brain structure involved in motor and cognitive functions.

Methods: We examined the effect of 4 different DR regimens (intermittent fasting and limited daily feeding of various onset and duration), on cholesterol metabolism in cerebellum of aging male Wistar rats. We used western blot to examine changes in the level of proteins playing the major roles in cholesterol biosynthesis (SREBP1 and HMGCR), transport (ApoE and LRP1) and elimination from the brain (CYP46).

Results: Detected changes in the expression level of selected proteins indicated that the effect of DR is highly dependent on the type of dietary regimen and the age when implemented. Positive effect is mainly noticed in the group of 18 months old rats.

Conclusions: This study showed the potential of dietary restriction as an alternative to pharmacological treatment of high blood cholesterol levels and confirmed beneficial effects of DR as a healthy lifestyle in prevention of age related disorders.

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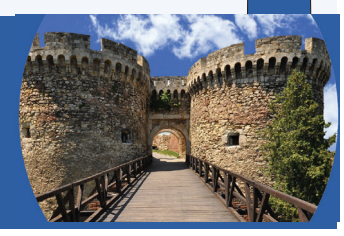

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P273

FUNCTIONAL AND PHARMACOLOGICAL ANALYSIS OF AGMATINE ADMINISTRATION IN DIFFERENT CEREBRAL ISCHEMIA ANIMAL MODELS

Radenovic Lidija[1], Arsenijevic Ljiljana[1], Selakovic Vesna[2], Stojanovic Marko[3], Radenkovic Miroslav[3], Andjus Pavle[1]

1Center for Laser Microscopy, Faculty of Biology, University of Belgrade, Serbia. 2Institute of Medical Research, Medical Faculty Military Medical Academy, University of Defense, Serbia. 3Department of Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Belgrade, Serbia

lidijar@bio.bg.ac.rs

Aims: Evaluation of agmatine effect in parallel at two animal models of cerebral ischemia - rat MCAO model and gerbil global ischemia model.

Methods: Agmatine (AgM, 100 mg/kg i.p.) was administrated 5 min after reperfusion in MCAO model (60'/24h, 60'/48h, 90'/24h, 90'/48h) and gerbil (10') model. Pharmacological analysis was performed on rat isolated common carotid arteries.

Results: AgM administration in MCAO significantly reduced infarct volume, improved neurological score and improved post-ischemic oxidative status (measured by Static Oxidation Reduction Potential). Results of behavioral tests (cylinder test, beam walking test, and adhesive removal test) have shown very effective functional recovery after AgM administration. Efficiency of AgM administration in gerbils was observed in cortex, striatum, hippocampus, and cerebellum at the level of each oxidative stress parameter (nitric oxide level, superoxide production, superoxide dismutase activity, and index of lipid peroxidation) measured in four different time points starting at 3 up to 48h after reperfusion. The highest levels were obtained 6h after the insult. The most sensitive oxidative stress parameter to AgM was nitric oxide. The pharmacological analysis of AgM on rat isolated common carotid arteries imply that mixed population of potassium channels located on smooth muscle cells was involved in common carotid artery response to AgM, with predominance of inward rectifying K+ channels.

Conclusions: As judged by behavioral, biochemical, as well as pharmacological data, the AgM administration showed a very effective reduction of ischemia-induced neurological damage as well as oxidative stress, hence moving us toward improving post-stroke recovery.

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P274

SOXB PROTEIN EXPRESSION IN THE HUMAN OLFACTORY EPITHELIUM: IMMUNOHISTOCHEMICAL STUDY OF PERIPHERAL NEUROGENESIS

Marija Schwirtlich[1], Nela Puškaš[2], Aleksandar Trivić[3], Miljan Folić[3], Sanja Krejović-Trivić[3], Danijela Drakulić[1], Nataša Kovačević-Grujičić[1], Isidora Petrović[1] and Milena Stevanović[1],[4],[5]

1 Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Belgrade, Serbia. 2 Institute of Histology and Embryology "Aleksandar Đ Kostić", School of Medicine, University of Belgrade, Belgrade, Serbia. 3 Clinic of Otorhinolaryngology and Maxillofacial Surgery, Faculty of Medicine, University of Belgrade, Belgrade, Serbia. 4 University of Belgrade, Faculty of Biology, Belgrade, Serbia. 5 Serbian Academy of Sciences and Arts, Belgrade, Serbia

schwirtlich@imgge.bg.ac.rs

Aims: SOX transcription factors have a critical role in regulating neurogenesis in adult central nervous system (CNS), including maintaining the multipotency and cell fate decision of neural stem/progenitor cells. However, their involvement in the regulation of peripheral nervous system neurogenesis is incompletely understood. The aim of the present study was to evaluate the expression pattern of the members of B group of SOX transcription factors in the olfactory epithelium where replacement of dying olfactory neurons occurs throughout lifetime.

Methods: Biopsies of olfactory mucosa were obtained from the area of the lateral superior wall of the nasal cavity of healthy individuals. The cellular distribution of selected SOXB proteins was studied by immunohistochemistry using standard indirect immunoperoxidase/ immunofluorescence protocols. Proliferating cells and olfactory neurons were identified by using specific antibodies for Ki67 and olfactory marker protein (OMP), respectively.

Results: Immunohistochemical analysis revealed distinct expression profiles of SOXB proteins in the cells of olfactory epithelium. While SOX2 and SOX21 proteins were abundantly expressed in progenitors, SOX3 protein was detected only in small number of cells. The expression of SOX1 protein was not detected.

Conclusions: Our results demonstrated that expression pattern of SOXB proteins in neural stem/progenitor cells in peripheral neurogenic niche resembles their distribution in neurogenic niches of CNS, suggesting important roles of these proteins in regulation of peripheral neurogenesis. Dysregulation of olfactory neurogenesis has been implied in numerous neurological disorders. Further studies are needed to evaluate SOXB proteins as potential biomarkers for neurogenesis under pathological conditions.

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P275

FLUOXETINE REVEALED SPECIFIC EFFECTS IN C-FOS PROTEIN EXPRESSION IN BRAIN SUBREGIONS OF CONTROLS AND CHRONICALLY SOCIALLY ISOLATED RATS

Stanisavljević Andrijana, Perić Ivana, Filipović Dragana

1Vinča Institute of Nuclear Sciences, University of Belgrade, Belgrade, Serbia

andristanisavljevic@vinca.rs

Aims: Fluoxetine (Flx) is an antidepressant of selective serotonin reuptake inhibitor class, currently in *use for treating* of depression. One of the animal models for studying anxiety- and depressive-like behaviours in rats is chronic social isolation (CSIS). The goal of the present study was to identify the activation of neural circuit, underlying chronic Flx treatment (15 mg/kg/day) in control and simultaneously applied in CSIS (3 weeks) rats, as well as, the effects of 3 weeks of CSIS alone. The c-Fos protein expression was used as a marker of neuronal activity.

Methods: Immunochistochemical detection of the number of c-Fos+ cells, in coronal sections of adult maleWistar rat's brain subregions, related to anxiety- and depression-like behaviours was done.

Results: Flx increased c-Fos protein expression in the retrosplenial cortex (RSC: granular and dysgranular), in the CA1, CA2 and DG-subregions of dorsal hippocampus (dHIPP), paraventricular nucleus of thalamus, posterior part (PVP), and lateral (LA)/basolateral (BL) complex of amygdala in controls. Flx applied simultaneously in CSIS revealed synergistic effects with CSIS and increased c-Fos protein expression in the dorsal CA field of HIPP, PVP, LA/BL complex of amygdala, dorsal (caudate putamen (CPu)) and ventral striatum (accumbens nucleus core and shell (AcbSh)). Moreover, CSIS alone increased c-Fos protein expression in the RSC, DG, PVP, LA/BL complex of amygdala, CPu and AcbSh.

Conclusion: We may suggest that dorsal CA fields, PVP, LA/BL complex of amygdala and dorso/ventral striatum may represent potential brain subregions of Flx action in anxiety and depressive-like behaviours.

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P276

THE ASSOCIATION OF VDR AND CYP2R1 GENES POLYMORPHISMS WITH PARKINSON'S DISEASE IN A GROUP OF SERBIAN PATIENTS

Luna Soso Zdravković[1], Eleonora Džoljić[2], Svetlana Ignjatović[3,4], Marija Sarić Matutinović[3], Jelena Veličković[1], Vladimir Kostić[2], Oliver Stojković[1]

1Institute of Forensic Medicine, Faculty of Medicine, University of Belgrade, Belgrade, Serbia. 2Neurology Clinic, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia. 3Department of Medical Biochemistry, Faculty of Pharmacy, University of Belgrade, Serbia. 4Center for Medical Biochemistry, Clinical Centre of Serbia, Belgrade, Serbia

lunasosozdravkovic@gmail.com

Aims: Risk and severity of Parkinson's disease (PD), neurodegenerative disorder that impairs dopaminergic signalization, have recently been associated with low serum vitamin D levels. The biological role of vitamin D is achieved through its activation by CYP enzymes, followed by its binding to vitamin D receptor (VDR). The aim of our study was to examine the association of polymorphisms in VDR and CYP2R1 genes with PD.

Methods: Our study included 114 patients suffering from PD, with measured serum level of vitamin D, and 59 healthy controls. All samples were genotyped for FokI (rs2228570) and TaqI (rs731236) in VDR, and rs10741657 in CYP2R1 genes.

Results: Our results showed that dominant model (AA+AG) of rs10741657, usually associated with increased level of serum vitamin D, imposes a greater risk for PD (OR-2.05; p=0.028), and that this risk is even greater in the group of patients with normal vitamin D level (OR-4.06; p=0.0081). The frequency of A allele was also higher in patients with normal vitamin D level compared to controls (OR-2.30; p=0.0131). The F allele and FF genotype of FokI show a trend towards significance (OR-1.75; p=0.0597 and OR-2.67; p=0.0873, respectively) when comparing patients with deficient vitamin D levels with controls.

Conclusions: Obtained results are the first evidence of significant association of CYP2R1 and VDR polymorphisms with PD in Serbian population. A slightly higher frequency of FokI implies that the increased activity of VDR, associated with F allele, could contribute to the risk for developing PD, which should be confirmed in further studies.

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P277

NEUROPROTECTIVE AND ANTI-INFLAMMATORY EFFECT OF GRAPHENE QUANTUM DOTS IN VITRO

Jelena Tasić[1], Sašenka Vidičević[1], Željka Stanojević[1], Nina Tomonjić[1], Aleksandra Isaković[1], Vladimir Trajković[2]

1Institute of Medical and Clinical Biochemistry, School of Medicine, University of Belgrade, Belgrade, Serbia. 2Institute of Microbiology and Immunology, School of Medicine, University of Belgrade, Belgrade, Serbia

jelena.tosic@med.bg.ac.rs

Aim: Aim of this study was to examine the potential cytoprotective and anti-inflammatory effect of graphene quantum dots (GQD) using co-cultures of olygo/neuron cells with activated ltmphocytes, since lymphocyte infiltration in central nervous system (CNS) induces demyelination, damage of axons, oligodendrocytes and neurons.

Methods: Olygodendrocytes (OLN93) and neuronal (PC12) cell lines were co-cultivated with lymphocytes in a presence/absence of GQD (50 μg/ml) for 48h. Lymphocytes (previously isolated from DA rats) were stimulated with ConA (5 μg/ml). In order to determine if GQD demonstrate anti-inflammatory or direct cytoprotective effect on CNS cells, commercial and primary oligodentrocytes/neurons were cultivated for 24h in a conditioned medium (25%) from unstimulated or ConA-stimulated lymphocytes in a presence/absence of GQD (50 μg/ml). Cell viability was determined by MTT assay while the expression of inflammatory mediators in ConA stimulated and GQD treated lymphocytes was examinated by qPCR.

Results: ConA stimulated lymphocytes significantly reduced viability of OLN93 and PC12 cell lines while GQD pretreatment alleviated its cytotoxic effect. Also, GQD exhibited direct cytoprotective effect on oligodendrocytes and neurons that were cultivated in conditioned ConA medium. In addition, GQD reduced the expression of mRNA for T cell mediators (IFN-γ and T-bet), TNF, IL-1β, GM-CSF and ROR-γt in ConA stimulated lymphocytes.

Conclusion: GQD protect oligodendrocytes and neurons from inflammatory mediated damage and reduce Th1 immune response in lymphocytes.

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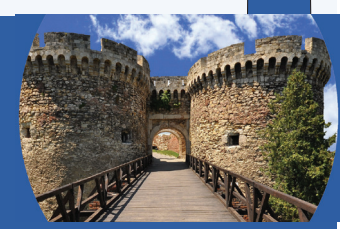

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MONONUCLEAR PHAGOCYTE SYSTEM IN TRAUMATIC BRAIN INJURY

Katarina Tešović[1], Irena Lavrnja[1], Marija Janjić[1], Iva Božić[1], Danijela Laketa[2], Sanja Dacić[2], Sanja Peković[1], Danijela Savić[1]

1Department of Neurobiology, Institute for Biological Research "Siniša Stanković", University of Belgrade, Belgrade, Serbia. 2Department for General Physiology and Biophysics, Faculty of Biology, University of Belgrade, Belgrade, Serbia

katarina.tesovic@ibiss.bg.ac.rs

Traumatic brain injury triggers neuroinflammatory response mediated by distinct populations of myeloid cells, including central nervous system (CNS) resident macrophages - microglia. Depending on the time upon insult this response may either contribute to restorative effects or hinder CNS repair.

Therefore, the focus of this study was on determining temporal course in gene expression profiles of markers specific to the mononuclear phagocyte system (MPS).

We have used the model of cortical stab injury which was performed on 3-months-old male Wistar rats. All animals were divided into 3 experimental groups: control, sham and lesion group and sacrificed at 1, 2, 3 and 7 days post-injury. After brain isolation, mRNA was extracted from cortical pieces around the center of lesion (the same tissue part was used for sham and control groups). The gene expression was analyzed by real-time PCR.

The mRNA levels of Itgam, Aif-1, Cd68 and Cx3Cr1, which are surface markers of MPS, were increased in first two days after brain injury, and then all, except Cd68, showed declining trend compared to control group. Furthermore, we analyzed expression of Arg-1, Il-6 and Tnf-alpha genes, which could be indicators of pro- or anti-inflammatory milieu. All of them increased significantly in the first two days post-injury, and then returned to control level, with the most prominent changes detected in Arg-1 mRNA level.

This study indicates enhanced MPS response in the acute phase after cortical stab injury. Further studies are required to determine which populations of CNS myeloid cells predominate in specific time point upon injury.

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INVESTIGATION OF CUPRIZONE INDUCED DEMIELINIZATION MECHANISMS IN VIVO AND IN VITRO

Sašenka Vidičević[1], Jelena Tasić[1], Željka Stanojević[1], Nina Tomonjić[1], Tamara Martinovic[2], Darko Ćirić[2], Aleksandra Isaković[1], Saša Petričević[1], Vladimir Trajković[3]

1Institute of Medical and Clinical Biochemistry, School of Medicine, University of Belgrade, Belgrade, Serbia;
2Institute of Histology and Embriology, School of Medicine, University of Belgrade, Belgrade, Serbia;
. 3Institute of Microbiology and Immunology, School of Medicine, University of Belgrade, Belgrade, Serbia

sasenka.vidicevic@med.bg.ac.rs

Aim: Investigation of cuprizone induced demielinization mechanisms in vivo (demyelinating animal model of Multiple sclerosis) and in vitro (oligodendrocytes and neurons), since cuprizone, as a copper chelator, could induce respiratory chain damage, oxidative stress and cell death.

Methods: In in vivo demyelinating model, Dark Agouti rats were divided into two groups, one receving cuprizone by food (0.6%) and another which did not receive cuprizone. After 6 weeks, demyelinization (using light microscopy and Luxol fast blue assay) and signal pathway of autophagy (Immunoblot) were examined in corpus callosum, cerebellum, spinal cord and cerebral cortex. Primary antibodies for pAMPK, pmTOR, beclin-1, p62, LC3II and actin were used. Immunoblot was also used to assess cuprizone effect on autophagy in vitro, in OLN93, PC12 and SH-SY5Y cells (1mM cuprizone, 6h,16h, 24h, 48h, 72h).

Results: Light microscopy confirmed that cuprizone leads to demyelinization. Immunoblot results revealed a decrease of autophagy activator pAMPK and increase of autophagy inhibitor pmTOR in cuprizone treated animals. Beclin-1, p62 and LC3II levels were not significantly changed. Immunoblot results, in vitro, demonstrated the same pattern of pAMPK and pmTOR changes while autophagy markers, LC3II, p62, beclin-1 did not show significant changes. These results indicate inhibition of autophagy, both, in in vitro and in vivo conditions.

Conclusion: Cuprizone leads to demyelinization, most likely by autophagy inhibition.

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P280

BRIEF CEREBRAL ISCHEMIA/REPERFUSION INJURY IN MALE WISTAR RATS AS A MODEL RELEVANT TO TRANSIENT ISCHEMIC ATTACK- EFFECTS OF ACUTE DEHYDROEPIANDROSTERONE TREATMENT

Marina Zaric[1], Dunja Drakulic[1], Milorad Dragic[1,2], Ivana Gusevac Stojanovic[1], Natasa Mitrovic[1], Ivana Grkovic[1], Jelena Martinovic[1]

1Department of Molecular Biology and Endocrinology, Vinca Institute of Nuclear Sciences, University of Belgrade, Belgrade, Republic of Serbia.
2Department for General Physiology and Biophysics, Faculty of Biology, University of Belgrade, Belgrade, Republic of Serbia

marinazaric@vin.bg.ac.rs

Aims: Disturbance of cerebral circulation may provoke transient ischemic attack (TIA) leading to a short-term neurological deficit without changes detectable using neuro-visualization methods. Despite major clinical relevance of TIA, appropriate animal model as well as effective therapeutic strategy is lacking. The primary aim of the study was to provide an animal model suitable for investigation of molecular alterations following mild ischemic conditions such as TIA. Seeking to potent therapeutic agent effects of neurosteroid dehydroepiandrosterone (DHEA) were investigated in physiological and ischemic conditions.

Methods: Adult male Wistar rats were treated with vehicle or DHEA (20 mg/kg i.p.) 4 h following sham operation or 15 min bilateral common carotid artery occlusion, performed to induce ischemia/reperfusion (I/R) injury. Neurological testing, 2,3,5-triphenyltetrazolium chloride staining of the whole brain and routine histological assessment alongside NeuN immunohistochemistry of hippocampus were carried out. Hippocampal cytosolic and mitochondrial Bax/Bcl2 protein ratio and mitochondrial membrane potential ($\Delta\Psi m$) were examined by Western blot and rhodamine 123 assay, respectively.

Results: Regular sensorimotor function, absence of cerebral infarcts through the whole brain and preserved gross neuronal morphology in HIP were observed in all experimental groups. DHEA showed no effects in physiological conditions, while its post-ischemic application resulted in alteration of Bax/Bcl2 ratio and $\Delta\Psi m$ dissipation.

Conclusions: I/R may serve as an appropriate model for investigation of molecular changes and treatment outcome following TIA. The study provided no evidence of previously reported neuroprotective DHEA effect and suggested exacerbation of I/R changes following the treatment which may lead to pro-apoptotic events.

Acknowledgement: The study was supported by the Ministry of Education, Science and Technological Development, Republic of Serbia, grants 173044 and 41014.

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P281

THE INFLUENCE OF SINGLE PROLONGED STRESS ON NEUROPEPTIDES - SUBSTANCE P, GALANIN AND ENKEPHALIN IN RATS' BRAIN

Zivkovic M[1], Djorovic Dj[2], Petrovic R[3], Aksic M[2], Velimirovic M[1], Stojkovic T[1], Petronijevic N[1]

1Institute of Medical and Clinical Biochemistry, School of Medicine University of Belgrade, Serbia. 2Institute for Anatomy, School of Medicine University of Belgrade, Serbia. 3Clinic for Psychiatric Illnesses "Laza Lazarevic", Belgrade, Serbia

drmilicazivkovic@gmail.com

Introduction: Single prolonged stress (SPS) presents an important animal model of posttraumatic stress disorder (PTSD), often occurring after life-threatening situations. In the central nervous system substance P is involved in processes leading to neuroinflammation while galanin acts as neuroprotective peptide. Endogenous opioids – enkephalins, act in pain suppression.

Aim: Assessing the influence of SPS on neuropeptides - substance P, galanin and enkephalin in rats' brain.

Material and methods: Twelve male Wistar rats, two months old, were divided into two groups: the first group that was subjected to single prolonged stress (SPS) and the other that represented control. SPS included: complete immobilization (2 h), forced swimming (20 min) and ether anesthesia (until loss of consciousness). Both groups were sacrified after 7 days. Neuropeptides were visualized with the immunohistochemistry method. Statistical significance was determined using Student T-test.

Results: Our results show statistically significant increase in the density of substance P-positive cells and statistically significant decrease in the galanin-positive cells in the PFC and amigdala in the experimental group compared to the control. No change has been observed for both peptides in the hippocampus. There was no statistical difference in the value of enkephalin-positive cells in either of the three examined structures.

Conclusion: Our results show that SPS leads to high and persistent neuroinflammation with deterioration of neuroprotective cells that are brain region specific. No change in the value of enkephalin-positive cells may implicate brains' inability to activate other protective mechanisms due to reverberation of signals in neuronal paths due to strong, life-threatening stress.

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P282

ANALYSIS OF RAT MITOCHONDRIA PROTEOM IN SELECTED HIPPOCAMPAL REGIONS AFTER BRAIN ISCHEMIC INJURY FOLLOWED BY REMOTE POSTCONDITIONING

Ľubica Mačáková, Jana Jachová, Petra Bonová, Rastislav Mucha, Miroslava Némethová

Institute of Neurobiology, Biomedical Research Center, Slovak Academy of Sciences, Košice, Slovakia

macakova@saske.sk

Brain ischemia (stroke) is one of the major civilization diseases that greatly reduces life or significantly aggravate its quality. Changes in brain tissue that occur during the absence of cerebral blood flow can lead to irreversible damage. One of the first altered reactions in neurons is the inhibition of protein synthesis which may be the cause of cell death. In selectively vulnerable regions of the brain occur the cells highly sensitive to oxygen deficiency and hence their metabolism can be reduced in the short time.

We have chosen CA1 and dentate gyrus – regions of rat hippocampus for our research.

The aim was to analyse changes in the mitochondrial proteome in 3 groups: control, ischemia and after remote postconditioning used. Postconditioning is a procedure that can induce neuroprotection and increased neuron´s resistance to cell death.

Samples were processed by protein extraction and separation by 2D differential electrophoresis and liquid chromatography with connection to MALDI TOF/TOF mass spectrometry. Data were analysed and evaluated using bioinformatics and statistics tools (MASCOT and ANOVA).

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P283

COMPARATIVE PROTEOMIC STUDY OF HEK-293 CELL LINE WITH INTRACELLULAR HYPOMAGNESEAMIA INDUCED BY THE OVEREXPRESSION OF MG2+ EXTRUDER SLC41A1

Pilchová Ivana[1], Tatarková Zuzana[2], Račay Peter[1,2], Kolísek Martin[1]

1Biomedical Center Martin, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovak Republic. 2Department of Medical Biochemistry, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovak Republic

iv.pilchova@gmail.com

Intracellular magnesium (Mg2+) homeostasis is maintained by complex network of transport mechanisms facilitating Mg2+ transport through membranes of cell and several subcellular compartments. Na+/Mg2+ exchanger SLC41A1 is currently the only known plasmalemal Mg2+ efflux transporter and its overexpression is associated with increased cellular Mg2+ efflux capacity leading to intracellular hypomagnesaemia.

The aim of our study was proteomic profiling of transgenic HEK-293 cell line with inducible overexpression of SLC41A1 together with its impact on cell viability and morphology.

Comparison of whole-cell proteome profiles was designed in time dependent manner to investigate the relation between changes on protein level influenced by intensity/duration of intracellular hypomagnesaemia revealing the most affected cellular metabolic pathways. Significant increase of SLC41A1 protein after induction of overexpression was observed already after 6h and the SLC41A1 accumulation was more intensive with prolonged incubation time (western blot). The negative impact on cell viability (MTT test) was evident after 48h of SLC41A1 overexpression. Whole cell protein profiles were prepared by 2D-SDS PAGE electrophoresis (0,1,3,6,16,24h) and after quantitative analysis were significantly deregulated proteins identified with MALDI-TOF/TOF mass spectrometer.

We identified in total 45 significantly deregulated proteins predominantly with binding and catalytic activity. The most affected cellular pathways included the cellular stress response, detoxification of reactive oxygen species and we identified also several proteins related to neurodegenerative processes.

Recently we published that SLC41A1 overexpression attenuate the anti-apoptic signaling cascade with impact on cellular physiology, however further molecular characteristics of SLC41A1 still needs to be investigated and translated into medical applications.

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PERIPHERAL BIOMARKERS OF TRAUMATIC BRAIN INJURY

Katarina Matyasova, Nikoleta Babindakova, Kristina Seserova, Peter Filipcik, Martin Cente

Institute of Neuroimmunology, Slovak Academy of Sciences, Bratislava, Slovakia

katarina.matyasova@savba.sk

Traumatic brain injury (TBI) is caused by an external physical force, which subsequently alters the brain function. TBI can be a reason of cognitive impairment, dementia and trigger other neurodegenerative conditions, such as chronic traumatic encephalopathy. The harmful consequence of repetitive mild TBI has been described in the brains of contact sport players who suffered by repeated concussive head impacts. After mild TBI, there might not be any immediately visible symptoms, what makes the diagnosis of cases of mild TBI difficult. Therefore, there is a need for a simple and reliable biofluid-based diagnostic test for TBI patients.

In our study we used digital-ELISA to perform analysis of protein biomarkers (neurofilament light chain and tau protein) in blood serum of athletes.

Results indicated altered dynamics of protein markers following high intensity exercise, heading and concussion. MiroRNAs (miRNAs) also represent potential peripheral biomarker. Specific miRNAs have been reported as dysregulated after TBI conditions.

This study is focused on finding valid molecular biomarker, for more precise diagnostics and follow up of symptoms after traumatic brain injury.

This project was supported by research grant: VEGA 2/0118/19, 2/0076/18, 1/0240/16, APVV-17-0668, ERA-NET NEURON RepImpact.

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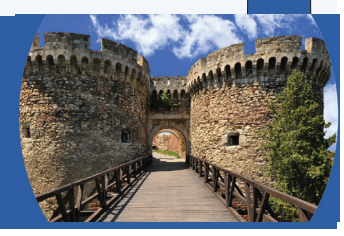

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P285

PERIPHERAL NON-CODING RNAS AS BIOMARKERS FOR ALZHEIMER´S DISEASE

Nikoleta Babindakova, Katarina Matyasova, Kristina Seserova, Peter Filipcik, Martin Cente

Institute of Neuroimmunology, Slovak Academy of Sciences, Bratislava, Slovakia

nikoleta.babindakova@savba.sk

The Incidence of Alzheimer´s disease (AD), the most common form of dementia, increases worldwide. MicroRNAs (miRNAs) as small non-coding RNA molecules have been shown to be involved in pathophysiology of AD. The role of miRNAs as post-transcriptional gene regulators and their stability in different biofluids (CSF, blood) signifies their perspective as valuable biomarkers for early AD diagnostics and treatment monitoring.

Main aim of this study is identification and validation of novel miRNA biomarkers in AD linked to the signalling pathways involved in the neurodegeneration.

To characterise expression profiles of miRNAs involved in AD pathways we performed transcriptomic analysis of AD individuals compared to healthy age matched controls.

We identified panel of dysregulated miRNA profiles clearly distinguishing the AD patients from healthy individuals.

Recent data suggest that panel of miRNA molecules could bring higher resolution for differential diagnostics of AD and related tauopathies.

This project was supported by research grant: VEGA 2/0118/19, 2/0076/18, 1/0240/16, APVV-17-0668, ERA-NET NEURON RepImpact.

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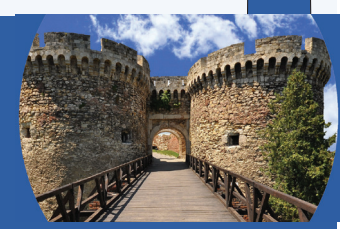

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P286

STROKE RESPONSE TO NON-ISCHEMIC REGIONS OF CONTRALATERAL HEMISPHERE IN ONE OF THE MOST COMMON MODEL OF TRANSIENT FOCAL ISCHEMIA IN RATS

Martin Bona[1], Natália Hvizdošová[2], Dalibor Kolesár[2], Janka Vecanová[2], Darina Kluchová[2].

1Department of Medical Physiology, Faculty of Medicine, Pavol Jozef Šafárik University in Košice, Slovakia. 2Department of Anatomy, Faculty of Medicine, Pavol Jozef Šafárik University in Košice, Slovakia

martin.bona@upjs.sk

Stroke induces widespread changes in the brain.

In present paper, we monitored some markers of early (protein synthesis activity and glutamate content) and delayed events (Iba1, CD68, NADPH-d, Fluro-jade C positivity) initiated by transient middle cerebral artery occlusion in core/penumbra counterparts of non-ischemic brain side (i.e. contra-core and contra-penumbra).

Our results showed, that profound transient drop (2 hours and 3 days) of protein synthesis up to 37.33% was measured in contra-core, while contra-penumbra exhibited translation over-activity at the same time (up to 29.73%). Glutamate release was detected only in contra-core with a peak at the first day of recovery. Degenerating neurons became visible in striatum (day 1), followed by ischemia more resistant cortex (day 3), earlier in contra-penumbra and later in contra-core. Moreover, stroke resulted in to the loss of NADPH diaphorase positive neurons in non-ischemic hemisphere, with the deepest drop one day after the attack. Total microglia started to fall as well. The earliest decline was evident in contra-penumbra region of striatum (day 1), followed by contra-core of striatum and both region of cortex seven day after the attack. Activated form of microglia was not detected in non-ischemic side of brain.

In conclusion, transient focal ischemia affects the distal regions of the brain and initiates processes involved in neuronal degeneration in order corresponding to tissue sensitivity to ischemia, earlier in contra-penumbra, afterwards in contra-core. The mechanism of secondary damage would influence on progressive neuronal loss in those distal brain regions.

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THE ROLE OF NO/SGC/CGMP SIGNALING IN RESPIRATORY NEUROPLASTICITY

Lukacova N, Hricova L, Bimbova K, Bacova M, Papcunova S, Stropkovska A, Kisucka A, Galik J
Institute of Neurobiology of Biomedical Research Center, Slovak Academy of Sciences, Košice, Slovakia

lukacova@saske.sk

The cervical spinal cord is the most common site of traumatic injury leading to interruption of descending respiratory pathway, which begins in the brainstem, innervates phrenic motoneurons (PhMN) in cervical spinal cord, and by the phrenic nerves (PhNs) controls the diaphragm.

The aim of our study was to find out whether this pathway is nitrergic.

In order to study NO/sGC signaling in brainstem–PhMN, C2-C3 hemisection was carried out. Unilateral PhNs ligation was used for identification of sGC/cGMP signaling in the lower respiratory pathway (PhMN-diaphragm). The animals (Wistar rats) survived 8 days. Immunohistochemistry, Western blot and ELISA were used to study changes in neuronal nitric oxide synthase (nNOS), the β1 subunit of soluble guanylyl cyclase (sGCβ1) and in level of cGMP.

C2-C3 hemisection caused strong reduction of nNOS fluorescent terminals around sGCβ1-immunoreactive PhMN on the side of the injury, significantly reduced sGCβ1 in contralateral PhMN and nearly abolished the sGCβ1 level in ipsilateral spinal cord. We also found an increase in sGCβ1 fluorescence signaling in PhMN on the side of the PhNs ligation. A significant decrease of the level of sGCβ1 protein in the PhNs below its ligation strongly reduced the cGMP level in the ipsilateral hemidiaphragm. Confocal analysis has shown a reduction of sGCβ1-immunoreactive terminals in ipsilateral neuromusclular junctions of diaphragm. Moreover, our results clearly show remarkable unilateral silencing of EMG activity after PhNs ligation and/or C2-C3 hemisection.

These findings indicate a role of NO/sGC/cGMP signaling in respiratory neuroplasticity.

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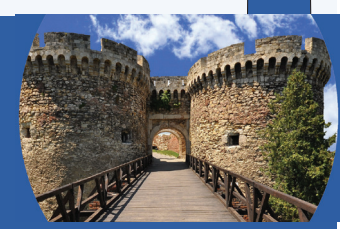

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P288

TWO DIFFERENT APPROACHES TO PROTEOMIC ANALYSIS OF RAT CA1 REGION AFTER BRAIN ISCHEMIC INJURY FOLLOWED BY REMOTE POSTCONDITIONING

Miroslava Nemethova[1], Sona Tkacikova[2], Lubica Macakova[1], Jana Jachova[1], Rastislav Mucha[1], Petra Bonova[1] and Ivan Talian[2]

1Institute of Neurobiology of Biomedical Research Center, Slovak Academy of Sciences, Kosice, Slovakia. 2Dept. of Medical and Clinical Biophysics, Faculty of Medicine, P. J. Safarik University, Kosice, Slovakia

nemeth@saske.sk

Aims: A promising approach to reducing ischemic damage and protecting neurons against injury caused by ischemia is the concept of inducing ischemic tolerance (IT). Although the mechanism of IT formation is not fully understood, it has been shown changes in gene expression as well as in protein levels induced by IT. We followed changes in protein patterns from rat CA1 hippocampal layer for elucidation of involved metabolic pathways through proteins identified.

Methods: Ischemia was induced in rats and upon its completion a tourniquet was applied on hind limb (remote postconditioning - RPostC). After 3 days of reperfusion brains were processed for proteomic analysis. Peptides were separated through nanoHPLC coupled to ion trap and to MALDI analysis, respectively. Proteins identified were compared to SwissProt database with 100 ppm tolerance for parental mass and 0.6 Da for ion fragments.

Results: In total, 215 proteins were identified in CA1 after RPostC application together; from these 172 proteins by MALDI and 98 by ESI. 67 proteins were present in overlapping of both analyses. Detailed analysis revealed 118 proteins uniquely identified by MALDI and 30 by ESI. Proteins detect by both approaches comprised compounds, which play a significant role in increasing activity of endogenous processes involved in neuronal protection against oxidative stress or were involved in elimination of toxic metabolic molecules.

Conclusions: Mass spectrometry as a useful tool for molecular processes and pathways study contributed to elucidation of brain endogenous mechanisms involved in cellular response to ischemic injury.

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P289

DIFFERENTIAL SUSCEPTIBILITY OF NEURONS AND ASTROCYTES TO MICROCYSTIN-LR

Klara Bulc Rozman, Maja Justin, Dušan Šuput

Institute of Pathophysiology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

klara.bulc@rozman.si; dusan.suput@mf.uni-lj.si

Aim: Industrialisation, intensive farming and climate changes have increased the occurrence of cyanobacterial blooms and consequently the occurrence of their toxins (e.g. microcystins) in our environment. Although MCs are considered primarily as hepatotoxins, several intoxicated individuals in Caruaru incident exhibited a variety of neurological symptoms. Our previous research showed MCs also induce DNA damage in the brain.

Methods: In order to clarify the apparent neurotoxicity of MC we investigated the effects of MC-LR on primary cultures of cortical neurons and primary mixed cultures of cortical neurons and astrocytes. Cell viability was assessed by MTT test, apoptosis by Annexin-V, propidium iodide and Hoechs. Immunocytochemistry was employed to confirm cell identity.

Results: MC-LR induced toxicity was time- and dose-dependent. The effect of MC-LR was prominent in mixed cultures where cell viability and cell number declined the most. Affected cells were rounded and lost their protrusions. Annexin-V labelling confirmed the apoptotic death of those cells. Labelling of neuron specific beta III tubulin and astrocyte specific glial fibrillary acidic protein (GFAP) showed little changes in neuronal morphology while astrocytes shrunk and their protrusions shortened. The results are in accordance with higher expression of Slco1b2 in mixed cultures, since Slco1b2 encodes the rodent Oatp1b2 that has been proven to transport MC-LR across cell membrane.

Conclusions: This study shows that astrocytes in culture are more susceptible to MC-LR induced toxicity than neurons. The loss of astrocytic homeostatic function could therefore be expected in the brain of intoxicated animals or individuals.

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P290

STRUCTURAL DETERMINANTS OF ALS-ASSOCIATED ANNEXIN A11

Vera Župunski[1], Jakob Rupert[1], Gregor Gunčar[1] and Boris Rogelj[1,2,3]

1Faculty of Chemistry and Chemical Technology, University of Ljubljana, Ljubljana, Slovenia. 2Department of Biotechnology, Jozef Stefan Institute, Ljubljana, Slovenia. 3Biomedical Research Institute BRIS, Ljubljana, Slovenia

vera.zupunski@fkkt.uni-lj.si

Aims: Recently, mutations in the annexin A11 gene (ANXA11) have been associated with amyotrophic lateral sclerosis (ALS), an incurable neurodegenerative disease of motor neurons. Annexin A11 is a member of annexin family of Ca2+-binding proteins with structurally conserved core domains and unique N-terminal domains. ANXA11 has the longest N-terminal domain of the family. To explain the functions of ALS mutations in ANXA11 we wanted to determine its crystal structure.

Methods: ANXA11 and its truncated forms were isolated from E. coli strain BLS21[DE3]pLysS using Ni2+-affinity chromatography and purified with gel filtration. Protein crystals were grown in Wizard solutions (Molecular Dimensions) and optimised for pH and salt. Diffraction data was collected at Elettra synchrotron in Trieste, Italy. We solved the crystal structure using molecular replacement.

Results: We have expressed and isolated 3 ANXA11 constructs: wild type and 2 truncated forms at N-terminal site. Structural predictions showed a high degree of intrinsic disorder in the proline and tyrosine rich N-terminal region of the protein. Only truncated ANXA11, lacking most of the N-terminal part. successfully crystallised. Crystals diffracted to 2,2 Å.

Conclusions: Structure of ΔN-ANXA11 has conserved core domain of 4 homologous annexin repeats with slight differences in the middle part. Prediction of disordered N-terminal domain explains unsuccessful crystal growth of the wild type and of the partially truncated N-terminal ANXA11. N-terminal part is too dynamic to enable crystal formation. Further analysis, based on the crystal structure of ANXA11 is needed to explain the changes of mutated forms in protein interactions and their functions.

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A2AR ANTAGONISTS POTENTIATE CB2R NEUROPROTECTIVE EFFECT IN ALZHEIMER DISEASE

Jasmina Jimenez[1,2], Rafael Franco[1,2], Irene Reyes[1,2], Dasiel Borroto-Escuela[3], Iu Raïch[1,2], Alejandro Lillo[1,2], Carlos Garcia[1], Anna Del Ser-Badia[4], Carles Saura[4], Kjell Fuxe[3], Enric I. Canela[1,2] and Gemma Navarro[2,5]

1Department of Biochemistry and Molecular Biology, University of Barcelona, Barcelona, Spain. 2CIBERNED. Centro de investigación en red en enfermedades neurodegenerativas. Instituto de Salud Carlos III. Madrid. Spain. 3Department of Neurosciences.Karolinska Institututed. Stockholm, Swden. 4Universitat Autònoma de Barcelona. 5Department of Biochemistry and Physiology, University of Barcelona, Barcelona, Spain

jasminajc@gmail.com

Aims: Microglia can be neuroprotective and, it is now considered -at least- two phenotypes of different cell types arising from activation of resting (or M0) cells: M1 or proinflammatory and M2 or neuroprotective. Among the four subtypes of adenosine receptors, the A2A is the most promising in neuroprotection. Moreover, A2A receptor (A2AR) antagonists are very safe and approved for Parkinson's disease treatment. Another receptor that may convey neuroprotective effects is the cannabinoid CB2 receptor (CB2R), that in the CNS is mostly expressed in glial cells.

Method: Bioluminescence resonance energy transfer (BRET) and Proximity Ligation Assay will be used to detect new heteromers as pharmacological targets for neurodegenerative diseases. Different signalling pathways (cAMP, MAPK phosphorylation, Dynamic Mass redistribution (DMR) and β-arrestin recruitment) will also be assayed.

Results: The results show that these two receptors can form heteromeric complexes (A2A-CB2Hets) in microglia, that A2A-CB2Hets are overexpressed in the brain of transgenic AD models and that A2AR antagonists enhance the action of endocannabinoids and of phytocannabinoids acting on CB2Rs.

Conclusion: A2AR antagonists could be used to block A2A receptor induced inhibition of cannabinoid neuroptotective effects, being an interesting target to treat neurodegenerative diseases.

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LONG-TERM SPORT PRACTICE INDUCES BRAIN RESILIENCE THROUGH SIRT1-SIRT3 AXIS IN MALE VETERAN RUGBY PLAYERS

Sanfeliu C[1], Corpas R[1], Solana E[2], De la Rosa A[3],Sarroca S[1], Griñán-Ferré C[4], Oriol M[5], Corbella E[6], Rodríguez-Farré E[1], Vina J[3], Pallàs M[4], Bartrés-Faz D[2], Gomez-Cabrera MC[3]

1Institut d'Investigacions Biomèdiques de Barcelona (IIBB), CSIC, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), and CIBERESP, Barcelona. 2Departament de Medicina, Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona, and IDIBAPS, Barcelona. 3Freshage Research Group, Department of Physiology, Faculty of Medicine, University of Valencia, and CIBERFES, Fundación Investigación Hospital Clínico Universitario/INCLIVA, Valencia. 4Unitat de Farmacologia i Farmacognòsia, Facultat de Farmàcia i Ciències de l'Alimentació, Institut de Neurociència, Universitat de Barcelona, Barcelona. 5Hospital Clínic, Barcelona. 6Unitat de Risc Vascular, Hospital de Bellvitge, IDIBELL, and CIBEROBN, Barcelona, Spain

coral.sanfeliu@iibb.csic.es

Aim: Physical exercise performed regularly is known to improve health and to reduce the risk of age-related diseases. We had previously reported improved immediate memory responses in a cohort of veteran rugby players as compared to control subjects with low physical activity. We hypothesized that long-term physically active middle-aged men have developed brain resilience that can be detected with the analysis of peripheral blood markers.

Methods: We tested the expression of selected genes of longevity, inflammation, redox homeostasis, and trophic signaling in whole blood mRNA. Analyses were performed on blood samples of veteran rugby players (n=24) and controls (n=25) aged 45-65 year, and also young controls (aged 15-25 years) with low physical activity (n=21). Physical activity and other lifestyles were thoroughly recorded with standardized questionnaires.

Results: Middle-aged control subjects showed lower levels of expression of SIRT1, SIRT3 and CAT than the young controls, although rugby players maintained the expression levels of these genes at a young-like level. No differences were detected in the inflammatory genes, although there was a tendency towards a decrease in trophic and transduction factors in middle-aged groups as compared to the young controls. A statistical study of Spearman's correlations supported a positive effect of sporting activity on memory and executive functions through SIRT1, SIRT3 and antioxidant gene expression levels in the veteran rugby players.

Conclusions: Our results suggest the involvement of the SIRT1-SIRT3 axis, and the downstream antioxidant and neuroprotective signaling, in the anti-aging resilience of the brain mediated by physical exercise.

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POSTER SESSION 2

P293

MECHANISMS OF NEUROPROTECTION OF SOLUBLE EPOXIDE HYDROLASE ENZYME INHIBITION IN ALZHEIMER'S DISEASE MODELS

Corpas R[1], Clotet N[1], Aguirre S[1], García-Lara E[1,2], Slevin M[2,3], Griñán-Ferré C[4], Galdeano C[6,7], Vázquez S[5,7], Suñol C[1], Pallàs M[4], Sanfeliu C[1]

1Institut d'Investigacions Biomèdiques de Barcelona (IIBB), CSIC, IDIBAPS, and CIBERESP, Barcelona, Spain. 2Targu Mures University of Medicine and Pharmacy, Targu Mures, Romania. 3Faculty of Science and Engineering, School of Healthcare Science, Manchester Metropolitan University, Manchester, United Kingdom. 4Pharmacology Section. Department of Pharmacology, Toxicology and Medicinal Chemistry, Faculty of Pharmacy and Food Sciences, Institut de Neurociències, University of Barcelona, Barcelona, Spain. 5Laboratori de Química Farmacèutica., Department of Pharmacology, Toxicology and Medicinal Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona, Barcelona, Spain. 6Department of Pharmacy and Pharmaceutical Technology and Physical Chemistry. Faculty of Pharmacy and Food Sciences, University of Barcelona, Barcelona, Spain. 7Institute of Biomedicine, University of Barcelona. Barcelona, Spain

rubencorpas@gmail.com

Aim: Chronic neuroinflammation associated with aging contributes to the onset and progression of Alzheimer's disease (AD). Epoxyeicosatrienoic acids (EETs) are endogenous mediators that have several protective functions including anti-inflammatory effects. EETs beneficial effects diminish when the enzyme soluble epoxide hydrolase (sEH) metabolizes them to the corresponding dihydroxyeicosatrienoic acids. Previous results showed that sEH inhibition mitigates cognitive impairment and AD-like brain pathology in SAMP8 and 5XFAD mouse models of senescence and AD, respectively. Here we investigate the underlying mechanisms of neuroinflammation and proteostasis changes related to cognitive loss and its neuroprotection by sEH inhibitors.

Methods: We used the known sEH inhibitor TPPU and the compound newly synthesized UB-EV-52. sEH inhibitors were administered through drinking water in the 5XFAD transgenic AD mouse models. In in vitro experiments, they were added to the media of microglia cell lines BV2 and HCM3, and neuroblastoma SH-SY5Y, previously treated with lipopolysaccharide or monomeric C- reactive protein as proinflammatory stimulus. As endpoints we analyzed inflammatory and survival pathways, and changes in proteostasis.

Results: Our findings confirmed the beneficial effects of sEH inhibition, reducing the cognitive impairment, increase of proteolytic mechanism against aberrant proteins with decline of Aβ and tau pathology, and decrease of inflammatory markers that suggests a protection against inflammaging. Moreover, UB-EV-52 agent showed higher inhibitory potency than TPPU and no cytotoxicity.

Conclusion: These results reinforce sEH as promising pharmacological target to fight against AD and other brain diseases that might be triggered by inflammaging processes.

Funding: SAF2016-77703, MINECO and ERDF; EU-COP 2014-2020, CRP-SAD, ID: P_37_674, MySMIS code: 103432, contract: 51/05.09.2016; 2017-SGR-106, AGAUR; Caixaimpuls 2018.

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EFFECT OF RECOMBINANT NEURAL AGRIN ON LONG-TERM CULTURE OF PRIMARY SKELETAL MUSCLE

Evgenii Bogatikov, Anna Rostedt Punga

Department of Neuroscience, Uppsala University, Uppsala, Sweden

evgenii.bogatikov@neuro.uu.se

Agrin is a neural transmitter that activates muscle specific tyrosine kinase (MuSK) at the skeletal muscle membrane and also induces nicotinic acetylcholine receptor (AChRs) clustering during development.

The aim of this study was to demonstrate the effect of recombinant rat agrin on clustering of AChRs in long-term culture of skeletal muscle cells.

We cultured differentiated C2C12 cells and primary skeletal myotubes from mice pups for more than 16 days in vitro. We applied recombinant rat agrin into cultured myotubes for 24h and measured AChR clustering by specific binding of fluorescently labelled α-Bungarotoxin.

We found that recombinant agrin promotes clustering of AChRs in both C2C12 and primary myotubes and can be applied in non-innervated skeletal muscle cell culture to compensate for any lack of neural agrin.

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NEURONAL PATHOLOGY IN A POLG1 GENETIC MUTANT OF PD

Chumarina M.[1,2], Russ K.[1,2], Azevedo C.[1,2], Heuer A.[3], Goldwurm S.[4,5], Roybon L.[1,2]

1Stem Cell Laboratory for CNS Disease Modeling, Department of Experimental Medical Science, BMC D10, Lund University, Lund, Sweden. 2Strategic Research Area MultiPark, Lund Stem Cell Center, Lund University, Lund, Sweden. 3Behavioural Neuroscience Laboratory, Department of Experimental Medical Science, BMC B10, Lund University, Lund, Sweden. 4Parkinson Institute, ASST Pini/CTO, Milan, Italy. 5Department of Neuroscience, Rita Levi Montalcini, University of Turin, Turin, Italy

margarita.chumarina@med.lu.se

Aims: Parkinson's disease (PD) is the most prevalent neurodegenerative movement disorder. Currently, the exact mechanism of its pathogenesis remains elusive, however, several cellular pathways have been linked to PD through the study of familial forms, which account for approximately 10% of all cases. Many PD-associated genes are known to be involved in disrupting mitochondrial homeostasis, suggesting an involvement of mitochondrial dysfunction in PD. A newly discovered link between mutations in mitochondrial DNA polymerase gamma 1 (POLG1) gene and parkinsonism may provide further insight into the role of mitochondria in neurodegeneration of dopaminergic (DA) neurons. Here, we investigate the phenotype-genotype relationship between parkinsonism and POLG1 through the use of induced pluripotent stem cells (iPSCs).

Methods: iPSC lines were generated from a female patient with parkinsonism, harboring a novel p.Q811R mutation in the POLG1 gene. iPSCs were then differentiated into neuronal cells enriched in DA neurons and used to assess cellular alterations compared to control lines derived from non-PD donors.

Results: Dopaminergic neuronal cultures of a midbrain phenotype were generated using a novel protocol that yielded 40% DA neurons. The identity of DA neurons was confirmed by co-expression of TH/FOXA2 and TH/VMAT2 markers. Measure of dopamine release using electrochemical detection methods revealed functional DA release upon KCL stimulation. A mitochondrial phenotype in DA neurons was observed in photomicrographs. Moreover, quantitative proteomics (LC-MS/MS) revealed alterations only in POLG1 DA neuron cultures when compared to control cultures.

Conclusions: Our results provide novel insights into PD pathogenesis, in particular, novel cellular pathways and mechanisms linking parkinsonism and mitochondrial dysfunction.

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THE EFFECT OF REDUCED RETROMER FUNCTION ON THE CLEARANCE AND TRANSFER OF INTRA- AND EXTRA-CELLULAR BETA-AMYLOID AND ALPHA-SYNUCLEIN IN NEURONS

Nazira J. Albargothy, Anna Ansell-Schultz, Christopher Sackmann and Martin Hallbeck

Division of Neurobiology, Clinical and Experimental Medicine (IKE), Linkoping University, Linkoping, Sweden

nazira.albargothy@liu.se

Aims: The vacuolar sorting protein 35 (VPS35) is a central component of the retromer system that is responsible for intracellular cargo sorting and recycling. Reduced expression and mutations in this protein were detected in the hippocampus of late-onset Alzheimer's disease (AD) and Parkinson's disease (PD) patients. The objective of this study was to determine the effect of reduced retromer function on the accumulation, transfer and clearance of oligomeric beta-amyloid and alpha–synuclein in neurons.

Methods: We established cell lines with reduced retromer function by selectively inhibiting VPS35 gene expression using si/shRNA in differentiated neuronal SH-SY5Y cells. Since VPS35 knockout is lethal, we also generated a cell line using CRISPR that expresses truncated VPS35 and lacks the functional domain of the protein. We then investigated the accumulation, transfer and clearance of oligomeric beta-amyloid.

Results: We show that reduced retromer function increases oligomeric beta-amyloid accumulation in neuronal cells and decreases clearance regardless if the oligomeric beta-amyloid originates from extracellular milieu or direct neuronal cell-to-cell transfer. The oligomeric beta-amyloid also colocalises with early endosome markers suggesting the involvement of the endocytic pathway.

Conclusions: These findings provide evidence that reduced retromer function decreases the ability of neurons to transport and clear neurotoxic beta-amyloid oligomers resulting in their accumulation. We predict that reduced retromer function will also result in the failure of alpha–synuclein clearance. Our data points to this system as an attractive therapeutic target to enhance the proper recycling and clearance of toxic oligomers to slow down or prevent disease progression.

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GENETIC MODULATION OF NEUROTROPHIN SIGNALING THROUGH THE P75 NEUROTROPHIN RECEPTOR

Ana Osório Oliveira[1], Carlos F. Ibáñez[1,2]

1Department of Cell and Molecular Biology, Karolinska Institute, Stockholm, Sweden;
2Department of Physiology, National University of Singapore, Singapore, Singapore

ana.oliveira@ki.se

Structural determinants underlying signaling specificity in the tumor necrosis factor receptor superfamily (TNFRSF) are poorly characterized, and it is unclear whether different signaling outputs can be genetically dissociated. The p75 neurotrophin receptor (p75NTR), is a key regulator of trophic and injury responses in the nervous system.

Here, we describe a genetic approach for dissecting p75NTR signaling and deciphering its underlying logic. Structural determinants important for regulation of cell death, NF-kB, and RhoA pathways were identified in the p75NTR death domain (DD).

Proapoptotic and prosurvival pathways mapped onto nonoverlapping epitopes, demonstrating that different signaling outputs can be genetically separated in p75NTR. Dissociation of c-Jun kinase (JNK) and caspase-3 activities indicated that JNK is necessary but not sufficient for p75NTR-mediated cell death. RIP2 recruitment and RhoGDI release were mechanistically linked, indicating that competition for DD binding underlies crosstalk between NFkB and RhoA pathways in p75NTR signaling.

These results provide insights into the logic of p75NTR signaling and pave the way for a genetic dissection of p75NTR function and physiology.

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P299

HOW DOES DOMESTICATION AFFECT THE HIPPOCAMPUS?

Jovana Malikovic[1,2], David P. Wolfer[1, 2], Lutz Slomianka[1,2], Irmgard Amrein[1, 2]

1Division of Functional Neuroanatomy, Institute of Anatomy, University of Zurich, Zurich, Switzerland. 2Department of Health Sciences and Technology, ETH Zurich, Zurich, Switzerland

jovana.malikovic@anatomy.uzh.ch

Aims: The domestication of mammals has led to an overall brain mass regression. The most prominent changes occur in the hippocampus. The hypothesis is that domestication changes requirements related to key functions of the hippocampus in memory, learning, emotions and spatial navigation. The hippocampus consists of five major cell populations: granule, hilar, CA3 and CA1 pyramidal cells, and subicular cells. Each of these cell populations serves a specific role in hippocampal information processing. We aim to define quantitative changes in these populations between domesticated species and their wild counterparts.

Methods: Estimated cell numbers of hippocampal subfields were obtained by a design-based stereological methods, the Optical Fractionator. The relationship between species and hippocampal cell population sizes were visualized using a correspondence analyses.

Results: The results show that taxonomically similar groups are separated in terms of the number of cells in different subfields of the hippocampus. Preliminary results indicate that both in foxes (family Canidae, Carnivora) and pigs (family Suidae, Artiodactyla) the strongest effects of domestication are seen in an increase of subicular cell numbers relative to other cell populations. Weaker effects are seen on hilar and CA3 cell numbers.

Conclusions: The results indicate that deprivation of natural environmental stimulation and behavioral transformations led to the changes in specific hippocampal cell numbers. The data allows us to study possible relationship between the different hippocampal subfields and ecological and life-history variables. Increasing the knowledge base of quantitative hippocampal cytoarchitecture is an important requirement for the functional understanding of the subfields.

P300

ESTROUS CYCLE EFFECTS ON NEURONAL CHROMATIN ORGANIZATION AND ANXIETY-LIKE BEHAVIOR

Ivana Jaric[1], Devin Rocks[1], John M. Greally[2], Masako Suzuki[2], Marija Kundakovic[1]

1Department of Biological Sciences, Fordham University, Bronx, NY, USA. 2Center for Epigenomics, Department of Genetics, Albert Einstein College of Medicine, Bronx, NY, USA

ivana.jaric@vetsuisse.unibe.ch

Aim: The prevalence of mood and anxiety disorders is twice as high in women as in men, and this difference is particularly evident during reproductive years. The cause of these sex differences is unknown although the role of sex-hormone fluctuations is assumed. However, information about underlying molecular mechanism(s) is missing. Here, we aimed to analyze how fluctuating sex-hormone levels affect neuronal chromatin accessibility and gene expression in order to better understand the mechanisms underlying female-specific vulnerability to anxiety and mood disorders.

Methods: We examined C57BL/6J female mice in two phases of the estrous cycle: diestrus (low-estrogen) and proestrus (high-estrogen), and compared them to aged-matched males. A test battery was performed to assess anxiety-like behavior. We then performed genome-wide assays to examine the effects of fluctuating sex-hormone levels on neuronal chromatin organization and gene expression in the ventral hippocampus, an area critical for emotion regulation.

Results: Female mice in the low-estrogen phase displayed higher anxiety-like behavior compared to high-estrogenic females and males. We observed significant differences in neuronal chromatin accessibility in the ventral hippocampus across the estrous cycle and between sexes. These differences are associated with the transcriptional activity of nearby genes important for neuronal function, neurotransmission, synapse formation, and behavior. Moreover, our data provide novel candidate genes and pathways underlying sex differences in anxiety-like behavior.

Conclusions: We show that chromatin organization in the female brain is remarkably dynamic during the estrous cycle. We link these dynamics to changes in anxiety-related phenotypes, providing mechanistic insights into sex differences in anxiety disorders.

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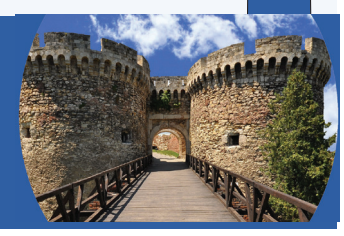

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P301

COMPARATIVE ANALYSIS OF MOUSE MODELS OF PARKINSON'S DISEASE BY MAPPING TRANSCRIPTOME DATA ON BRAIN METABOLIC NETWORK

Ecehan Abdik, Tunahan Çakır

Gebze Technical University, Bioengineering, Kocaeli, Turkey

ecehanabdik@gmail.com, tcakir@gtu.edu.tr

Aims: A genome-scale metabolic network, a list of all reactions in the metabolism of the cell of interest, was proven to be very useful to model metabolic behaviors and pathway activities of organisms. Such a model was previously reconstructed for neuron-astrocyte coupled brain metabolism in human. However, a brain-specific metabolic network for Mus musculus (mouse), which is the most commonly used model organism for neurological diseases, is not available yet. The aim of this study is reconstructing a brain-specific metabolic network at genome-scale to investigate two animal models of Parkinson's Disease (PD) in terms of their prediction of disease effects on metabolism.

Methods: Brain-specific mouse metabolic network model was reconstructed by a homology based approach using the available human brain network as a template. The final model includes 585 genes controlling 871 reactions, distributed over 107 pathways. The transcriptome data of MPTP injected mouse model and Pink1 knockout mouse model of PD were obtained from Gene Expression Omnibus database and mapped on the reconstructed metabolic network to predict reaction rates. The quality of the animal models to reflect the metabolic changes in PD state were tested comparing the control and disease groups.

Results: Predicted glutamine-glutamate cycle, O2 consumption, TCA cycle and lactate production rates were used as representatives of PD affected pathways. It was shown that MPTP injected PD model reflects the PD metabolism more realistically than the Pink1 deleted model does.

Conclusion: The computational modeling approach can predict the changes in mouse brain metabolism in PD animal models. Using human and mouse versions of the brain-specific metabolic models comparatively can serve as a new approach to develop better mouse models for PD.

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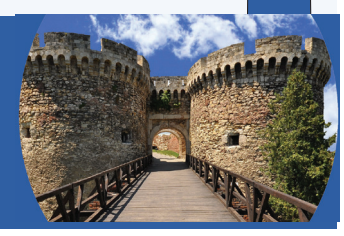

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P302

NO-DONOR STIMULATION EFFECTS GLIAL CELL IRON HOMEOSTASIS DIFFERENTLY IN CELL CULTURE

Arzu L. Aral[1,2], Hayrunnisa Bolay Belen[2]

1Gazi University Faculty of Medicine Department of Immunology, Turkey. 2Gazi University Neuropsychiatry of Education, Research and Application Center, Turkey

arzuaral@gmail.com

Aim: Although at physiological level, iron plays role in a wide variety of cellular mechanisms; if presented excessively in cells, it causes oxidative stress and cell damage. The proper homeostasis of cellular iron transport and storage proteins are important to prevent excess iron overload or iron starvation. Oxidative stress and NO, as triggering factors of migraine, may cause cellular accumulation and mislocalization of iron. The aim of this study is to investigate the NO-stimulated cellular iron transport and storage and cytokine levels in glial and meningeal cell culture.

Methods: Primary cell cultures were prepared from cerebral cortex of neonatal C57BL/6 mice. Cells were stimulated with glyceryl trinitrate (GTN) as NO donor for 24h. Effects of GTN on expression of iron transport and storage proteins were evaluated by qPCR. Cellular iron accumulation was evaluated using Perl's histochemistry. Ferritin protein in cells was assessed using immunofluorescence staining. NO, IL-6, IL-10 and MMP-9 levels in cell culture were evaluated using ELISA.

Results: GTN stimulated expression of ferritin in all cell types. Histochemical staining of accumulated iron in the cells was more prominent in meninges. Ferroportin expression was increased in microglia and meningeal cells but not in astrocytes. GTN stimulation increased IL-10 and MMP-9 levels in astrocytes significantly.

Conclusion: Incubation with GTN stimulates iron accumulation in several cell types and triggers the expression of iron homeostasis proteins differently. NO donor may have a significant effect on the migraine process by affecting iron homeostasis and cytokine profile in meningeal cells and parenchymal glia, through, depot and carrier iron proteins.

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P303

ACTIVATION OF SONIC HEDGEHOG ENHANCES SURVIVAL OF NEURONS VIA INHIBITION OF GRP78-DEPENDENT PATHWAY IN BRAIN OF DIABETIC MICE

Nuriye Ezgi Bektur Aykanat, Sedat Kaçar, Erhan Şahin, Varol Şahintürk

Department of Histology and Embryology, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey

nebektur@ogu.edu.tr

Aim: Eukaryotic cells have a signaling pathway called the unfolded protein response (UPR) to adhere to ER stress conditions. The dysfunction of UPR causes neurodegenerative, metabolic, inflammatory diseases and diabetes mellitus. Therefore, ER stress-related signaling pathways can serve as strong therapeutic targets for ER stress-related diseases. This study was carried out to determine the association of sonic hedgehog (Shh) activator and inhibitor substances with ER-stress marker GRP78 expression in diabetic mice.

Methods: Sixty male mice were divided into six groups. The control group mice were given citrate buffer only. Mice were injected intraperitoneally with streptozotosin (STZ) at a dose of 40 mg/kg for 5 consecutive days for diabetic group. After 6 weeks of STZ injection, 3.3 mg/kg Shh inhibitor (SANT-1) was given for 14 days for diabetes + SANT-1 group and 5 mg/kg Shh activator (SAG) for diabetes + SAG group intraperitoneally. Mice in the last two groups received 5 mg/kg SAG or 3.3 mg/kg SANT-1 alone intraperitoneally for 14 days. At the end of the experiment, GRP78 expressions were measured by immunohistochemistry and western blot in the brain tissue.

Results: Diabetes causes an increase in the expression of GRP78 in the brain tissue, thus causing ER-stress. SAG and SANT administration to diabetic mice resulted in decreased GRP78 while only SANT causes an increase and only SAG was not effective.

Conclusions: These findings indicate that diabetes activates ER-mediated pathway through GRP78. In contrast to their use alone, inhibition or activation of Shh expression causes reduction in ER-stress in diabetes.

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P304

THE EFFECT OF ADRENALIN-INDUCED MESENCHYMAL STEM CELL TRANSPLANTATION ON PERIPHERAL NEUROPATHY

Fatih Berktaş[1], Erkan Maytalman[2], Leman Sencar[3], Olcay Kıroğlu[1]

1Department of Medical Pharmacology, Çukurova University, Turkey. 2Department of Medical Pharmacology, Alanya Alaaddin Keykubat University, Turkey. 3Department of Histology and Embriology, Çukurova University, Turkey

eczfatih01@hotmail.com

Aims: We aimed to investigate the regenerative effects of induced mesenchymal stem cells (MSCs) by adrenergic stimulation in peripheral neuropathy formed in mice.

Methods: Peripheral neuropathy was formed by partial sciatic nerve ligation in mice. MSCs and MSC induced by adrenergic system agonists and antagonists (adrenoceptor agonist adrenaline, β-adrenoceptor blocker propranolol and α-adrenoceptor blocker phentolamine) were administered to the lesions. Rotarod for motor function and cold plate latency test (CPL) for cold allodynia were performed on the fourth, sixth, eighth and tenth week in all groups. Histopathological examination of the sciatic nerve and soleus muscle isolated at 10th week. Results were analyzed using one way ANOVA followed by the Bonferonni post hoc test. This study is supported by Çukurova University Research Foundation (TYL-2016-7543).

Results: In the rotarod test, there was an increase in motor functions and in terms of time compared to the neuropathy group in MSC and induced MSC groups. In the CPL test, compared with the neuropathy group it was measured that the increase in cold allodynia threshold was related to time in MSC and induced MSC groups. Histopathological examination showed significant improvement in tissues according to neuropathy group in MSC and induced MSC groups. However all data was determined that the α-adrenoceptor antagonist treatment group had less improvement.

Conclusions: This study demonstrates that adrenergic stimulation induced MSCs in peripheral neuropathy are located in the damaged nerve region, proliferate and regenerate nerve tissue. This results show that α-adrenoceptors have migth a role in proliferative and regenerative affect of induced MSCs.

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P305

PYCNOGENOL HIGH DOSE DECREASED GLUTAMATE INDUCED TOXICITY: IN VITRO STUDY

Betul Cicek[1], Ali Taghizadehghalehjoughi[2], Ahmet Hacimuftuoglu[3]

1Department of Physiology, Ataturk University Faculty of Medicine, Erzurum, Turkey. 2Department of Pharmacology and Toxicology, Ataturk University Faculty of Veterinary Medicine, Erzurum, Turkey. 3Department of Medical Pharmacology, Ataturk University, Faculty of Medicine, Erzurum, Turkey

bcicek_24@hotmail.com

Aims: Glutamate is a major neurotransmitter in the central nervous system. However, elevated levels of glutamate result in neuronal excitotoxicity and is linked to neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Pycnogenol is a herbal medicine with antioxidant and antiinflammatory properties. This study was designed to investigate the neuroprotective effect of pycnogenol against glutamate-induced excitotoxicity in the primary cultured cortical neurons.

Methods: Primary cortical neuron cells were grown in the suitable cell culture media. Glutamate (10-5 mM) was added to the culture medium for 20 min to induce excitotoxicity. The neurons were exposed to different concentrations of pycnogenol (10-1 - 10-5) for 24h. The MTT assay was used to detect cell viability. TAS-TOS analysis was performed to evaluate antioxidant and oxidant status.

Results: According to MTT analysis results, it was found that 10-1 and 10-2 pycnogenol groups significantly attenuated the glutamate excitotoxicity induced cell damage. Pycnogenol applied at a dose range of 10-3 - 10-5 were found to have cytotoxic effects on cell viability compared to control group ($p<0.05$, $p<0.001$). Furthermore, TAS-TOS analysis showed a correlation with MTT result.

Conclusion: It has been determined that pycnogenol has neuroprotective effect on glutamate excitotoxicity in a dose-dependent manner. Its mechanism of action is likely associated with its antioxidant activity, as demonstrated by its ability to decreased TOS levels as well as increased TAS levels. These results may provide a new potential therapeutic target for glutamate excitotoxicity. However, further studies are required to clarify the detail mechanisms of the neuroprotective effects of pycnogenol.

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P306

INVESTIGATION OF MOTOR BEHAVIORS AND DENSITY OF LOWER MOTOR NEURONS IN RATS FOLLOWING TRANSFER OF TRANSGENES ENCODING TDP-43 USING IN UTERO ELECTROPORATION

Ercelen B[1], Brent J[2], Ozdinler PH[2], Ulupinar E[1,3]

1Department of Anatomy, Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey. 2Department of Neurology, Feinberg School of Medicine, Northwestern University, Chicago, USA. 3Interdisciplinary Neuroscience Department, Health Sciences Institute, Eskisehir Osmangazi University, Eskisehir, Turkey

ercelenbirce@gmail.com

Aims: TAR-DNA binding protein-43 (TDP-43) is a nuclear protein playing crucial roles in many cellular processes. It has also been shown in the etiopathogenesis of several neurodegenerative diseases, including motor neuron diseases. The aim of this study was to investigate motor behaviors and density of lower motor neurons in rats following transfer of transgenes encoding TDP-43.

Methods: In utero electroporation was used to transfer DNA (1µg/µl), encoding full length or mutated TDP-43 protein tagged with GFP under the CBA promoter, on embryonic day (E) 17,5. The motor cortex area was targeted using a triple-electrode probe (intensity:50V, duration:50ms, interval:150ms). Motor behaviors of pups were evaluated by modified string suspension, rotarod, catwalk and locomotor activity tests between P60-P300. Quantification of motor neurons were done in sections obtained from cervical (C5-6) and lumbar (L5-6) spinal cord segments.

Results: Total number of movements in spontaneous locomotor activity, latency of falling in rotarod and performance in modified string suspension test displayed a progressive decline in transgenic rats beginning at P60. The density of lower motor neurons in C5-C6 segments was not significantly different among groups. However, a significant decline was observed in in L5-L6 segments of animals transfected with full-length or mutated TDP-43 in comparison to control animals.

Conclusions: Transgene expression of TDP-43 in rat embryos causes lower motor neurons degeneration and progressive loss of motor functions in adult rats. In utero electroporation technique is a valuable tool for investigating motor neuron pathology subsequent to rapid and efficient delivery of different transgenes in rat embryos.

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P307

MELATONIN REDUCES OXIDATIVE STRESS AND RAGE LEVELS IN DIABETIC RATS

Meryem Ergenc, Hale Sayan Ozacmak, Incı Turan, Veysel Haktan Ozacmak

Zonguldak Bulent Ecevıt Unıversıty Faculty of medıcıne, department of physıology, Zonguldak, Turkey

meryemergenc@gmail.com

Aims: Diabetes Mellitus (DM) is a metabolic and endocrine disease that causes acute and chronic complications. Hyperglysemia causes increase in the synthesis of advanced glycation end products (AGE), receptor for AGE (RAGE) and oxidative stress in brain areas, such as hippocampus and prefrontal cortex (PFC) in streptozotocin (STZ)-induced diabetic rats. It has been demonstrated that elevated levels of RAGE increase the synthesis of oxygen free radicals and increased oxidative stress stimulate more RAGE production, thus causing to a positive feedback loop. Melatonin is a potent antioxidant agent secreted from the pineal gland. In this study, we examined the therapeutic potential of melatonin in oxidative stress as well as levels of RAGE in PFC and hippocampus of diabetic rats.

Methods: Diabetes was triggered by a single intraperitoneal (i.p.) injection of STZ (60 mg/kg). Animals were divided in 4 groups each of 8 animals: Normoglisemic; Normoglisemic+melatonin; diabetic; diabetic+melatonin (10 mg/kg/day, for 4 weeks). Malondialdehyde (MDA), vitamine C, and reduced glutathione (GSH) contents were measured for analysis of oxidative stress in the PFC and hippocampus. The levels of RAGE were also measured.

Results: Our results demonstrated that diabetes increased the contents of MDA, and RAGE while decreasing those of GSH and vitamine C levels. Melatonin treatment was effective normalizing the levels of GSH and vitamine C, decreasing levels of MDA and RAGE.

Conclusions: Our results displayed that melatonin administration may exert antioxidant effects in diabetic rats through normalizing of RAGE and oxidative stress in the PFC and hippocampus.

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P308

CORRELATION BETWEEN HAMMERSMITH EXAMINATION SCORE AND COPY NUMBER OF SMN2 GENE IN ADULT PATIENTS WITH SPINAL MUSCULAR ATROPHY

Güleç R.[1], Koç F.[2]

1Cukurova University,Institute of Natural and Applied Sciences,Biotechnology. 2Department of Neurology, Çukurova University,Faculty of Medicine, Adana, Turkey

rbglc6@gmail.com

Aıms: This study aimed to compare the number of SMN2 gene copies and Hammersmith score of patients with Spinal muscular atrophy,using molecular and functional methods.

Methods: Spinal muscular atrophy is a neuromuscular disorder caused by production of unsufficient level of survival motor neuron (SMN) protein.Patients have a homozygous deletion or mutation in the SMN1 gene, SMN gene has a copy called SMN 2,but it produces very little functional SMN protein induced by a mistake during RNA editing(exon skipping). The study included 21 cases, who applied to the neurology department and were diagnosed with spinal muscular atrophy through clinical, laboratory, and electrophysiological findings, their genetic analyses(using MLPA methods) were performed. Pedigree was drawn, neurological examination was performed for all cases.

Results: Total of 21 patients, who were 19–41 years of age. There wasn't similar distribution across the sexes with 18 males and 3 females assessed. The median age at assessment was 32 years 6 months. The average Hammersmith score was 33.8. The scores were normally distributed with a minimum of 0 and a maximum of 55. Most of the patients contained 3(9 patients) or 4(10 patients) copies of SMN2.

Conclusıon: SMA patients which have deletions of SMN1 and patients with higher SMN2 copy numbers had milder form of disease than those patients with fewer copies(2 patients have 2 copies)of SMN2. There wasn't correlation between SMN2 copy number and Hammersmith score in this group.

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ROLE OF NMDA-2B RECEPTOR SUBTYPE IN THE PROCONVULSANT EFFECT OF CINNAMALDEHYDE IN RATS

Caner Günaydın, S. Sırrı Bilge

Ondokuz Mayıs University, School of Medicine, Deparment of Pharmacology, Samsun, Turkey

gunaydincnr@gmail.com

Introduction: Cinnamaldehyde is a naturally occuring flavonoid in the bark of cinnamon trees and other species of the cinnamomum. It has potent anti-inflammatory and anti-oxidant effects on various studies. However, the effects of cinnamaldehyde in experimental epilepsy models is unknown. The main goals of the present study were to obtain the effects of cinnamaldehyde and clarify responsible mechanism in the PTZ(Pentylenetetrazol) induced kindling model of epilepsy in rats.

Materials and methods: Adult, male Sprague-Dawley rats (weighing 220-260 g) were randomly selected as six number per groups. Kindling were induced by injection of PTZ (35 mg/kg, i.p.) at every other day (Mean injection number = 13). The animals were considered to be kindled after exhibiting at least three consecuvite stage 4 or 5 seizures then kindled animals were placed in stereotaxic apparatus and bi-polar electrodes were positioned for electrocortical recordings. After baseline recordings cinnamaldehyde (10 mg/kg, 30 mg/kg, i.p.)(Sigma Chemical Co., St. Louis, MO), was administered 14 day. After twent-four hours of last drug treatment, recording was repeated and animals were sacrificed for western blot analysis. Differences between groups were analysed with SPSS (v20) using One-way analysis of variance (ANOVA) and $p < 0,05$ was accepted as significant.

Results: Cinnamaldehyde (10 mg/kg, 30 mg/kg) administration increased behavioral seizure stage and spike numbers and decreased first myoclonic jerk time significantly compared to control group ($p < 0,05$). Additionally, cinnamaldehyde administration caused an increase in NMDA-2B receptor and CREB expression more than control group which was statistically, significant ($p < 0,05$).

Discussion: In present study, ingredient of commonly used spice of cinnamon, showed proconvulsant effect in the kindled animals. Increased cellular NMDA-2B and CREB response is possible mechanism of pro-convulsant action of cinnamaldehyde.

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CYTOARCHITECTURE OF THE HUMAN SPINAL CORD

Buse Kayhan[1]*, Seyhmus Bayar[1], Esra Candar[1], Mahmud Mustafa Özkut[2], Pelin Çoruk[1], Gulgun Sengul[3]

1Department of Neuroscience, Institute of Health Sciences, Ege University, Izmir, Turkey. 2Department of Histology and Embryology, School of Medicine, Yozgat Bozok University, Yozgat, Turkey. 3Department of Anatomy, School of Medicine, Ege University, Izmir, Turkey.

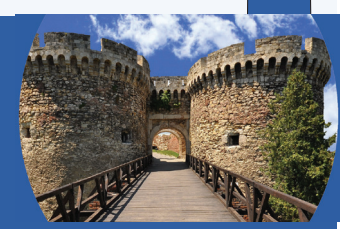
kayhanbuse@gmail.com

Aims: Neurons in the spinal cord use a variety of neurotransmitters to carry out their functions, and they in turn receive a variety of neurotransmitter inputs. These neurotransmitters show distinct patterns of distribution within the spinal cord that are similar across different species. In this study, neurotransmitters of the human spinal cord have been identified by histochemical localization of their synthesizing and degradating enzymes, as well as using immunocytochemistry.

Methods: In the human spinal cord, we used immunohistochemical and histochemical techniques on 60 µm thick transverse spinal cord sections cut on a cryostat.

Results: We have observed glutamate receptor immunoreactivity throughout the spinal cord laminae 1–9, area 10, intermediolateral nucleus and dorsal nucleus (of Clarke) in humans, GABA mainly laminae 1-3, substance P in laminae 1-5, CGRP in laminae 1–3, 5, area 10, neuropeptide Y concentrated in the intermediolateral and sacral parasympathetic nuclei, 5-HT receptors in the ventral horn, intermediolateral nucleus, and ventral horn, ChAT in laminae 1–2, 9, and in the intermediolateral and sacral parasympathetic nuclei, CART in intermediolateral and sacral parasympathetic nuclei, and NOS in the intermediolateral and sacral parasympathetic nuclei, in laminae 1, 2, and area 10.

Conclusion: This is the first systematic study for the distribution of major neurotransmitters of the human spinal cord.



P311

THE IMMUNOHISTOCHEMISTRY AND MORPHOLOGY OF GLUTAMATERGIC AND CHOLINERGIC AXONS SYNAPSING ON TASTE THALAMUS NEURONS

Elif Keskinöz, Erin Maher, Alev Erisir

Acibadem Mehmet Ali Aydinlar University, Istanbul, Turkey. 2University of Virginia, Charlottesville, VA, USA

elifk2007@gmail.com

The glutamatergic axons that bring the primary excitatory input onto relay cells in visual, auditory and somatosensory thalamic nuclei are distinct in that they utilize Vesicular Glutamate Transporter Type 2 (VGluT2), whereas those bringing the corticothalamic excitatory feedback utilize VGluT1. In addition, a cholinergic input from the brainstem modulates the excitability of the relay cells.

We asked whether these properties common in non-chemical sensory pathways were also the characteristics of the relay cells of the thalamic nucleus that represents the chemical sense, taste.

We examined the tree shrew taste thalamus, VPMP, using immunocytochemistry approaches with VGLUT2, VGLUT1 and ChAT antibodies, and electron microscopy.

We found VGluT2 in terminal boutons that were large, and they contained multiple mitochondria and unstained dendritic protrusions. Similar to primary excitatory axons found in non-chemical thalamic nuclei, these terminals formed asymmetric synapses on multiple dendritic profiles, engaged in triadic arrangements, and often located in glomerular complexes, surrounded by glial sheets. The VGLuT1 containing terminal boutons were plenty and small in size and these formed single, asymmetric synapses on small-caliber dendrites. The ChAT positive terminals were medium in size, and these were also found outside of glomerular structures. Quantitative analysis of terminal cross-section areas revealed that VGluT1 + terminals were the smallest in size, consistent with morphological properties of corticothalamic axons.

The morphological and molecular properties of glutamatergic and cholinergic terminals in taste thalamus of the tree shrew lend evidence for conservation of the design principles across the sensory thalamic nuclei.

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NEUROPROTECTIVE POTENTIAL OF STRIGOLACTONES ON LPS-ACTIVATED BRAIN ENDOTHELIAL AND MICROGLIAL CELLS

Begum Kurt[1], Adem Ozleyen[1], Elif Turkdonmez[1], Gizem Antika[1], Berkay Yilmaz[1], Tugba Boyunegmez Tumer[2]

1Graduate Program of Biomolecular Sciences, Institute of Natural and Applied Sciences, Canakkale Onsekiz Mart University, Canakkale, Turkey.
2Department of Molecular Biology and Genetics, Faculty of Arts and Science, Canakkale Onsekiz Mart University, Canakkale, Turkey.

begum@stu.comu.edu.tr

Aims: Neurodegenerative diseases are functional disorders that commonly described by the lack of behavioral, cognitive or motor skills. Most neurodegenerative diseases are related with microglia or blood-brain barrier deficiency-caused neuroinflammation. In the brain, reactive oxygen species (ROS) are key signaling molecules that play an important role in the progression of the inflammatory response. The excessive amount of ROS production may cause persistent inflammation in glial and endothelial cells. NF-E2-related factor 2 (Nrf2), a transcription factor and a key regulator, is responsible for the expression of many anti-oxidants and phase II detoxification enzymes as defense mechanism. In this study, we showed that GR24 have a potential neuroprotective molecule by inducing Nrf2 and nrf2-related cytoprotective enzymes.

Methods: Cultured SIM-A9 microglia and bEnd.3 brain endothelial cells were treated with GR24 at 10 and 20 μM in the presence of LPS, then the cytoprotective effects of GR24 on these cells were determined at both mRNA and protein expressions level by real-time PCR and Western Blot analysis.

Results: In microglia cells, GR24 at 10 20 μM dramatically induced Nrf2 protein expression level by 93% and 52%, and mRNA expression level by 13% and 50%, respectively compared to LPS-induced control group. The same doses of GR24 significantly induced the up-regulation in the mRNA expression of Nrf2 and downstream enzymes HO-1 by 1.5-fold and 2.4-fold, NQO1 by 9.5-fold and 13-fold, respectively. On bEnd.3 brain endothelial cells, GR24 at 10 μM and 20 μM doses markedly increased the mRNA expression of NQO1 by 3.19-fold and 3.27-fold, respectively.

Conclusion: Considering these findings, GR24 may be a promising cytoprotective agent for ROS-dependent neurodegenerative disorders and it could be a candidate molecule for the treatment or/and prevention of neuroinflammatory/neurodegenerative diseases.

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A COMPARTMENTAL 3D SCAFFOLD FABRICATION AND ALIGNMENT DEVICE FOR NEUROVASCULAR CO-CULTURE AND TRI-CULTURE

Fulya Ersoy[1], Emel Sokullu[2]

1Department of Biomedical Technologies, Graduate School of Natural and Applied Sciences, Izmir Katip Celebi University, Izmir, Turkey.
2Department of Engineering Sciences, Division of Bioengineering, Izmir Katip Celebi University, Izmir, Turkey

emelsu@gmail.com

The aim of the study was to create an easy-to use device to fabricate precisely designed 3D hydrogel scaffolds for co-culturing, tri-culturing and multi-culturing practices.

In this study, gelatin methacrylate (GelMA) was synthesized and textured three-dimensional hydrogel scaffolds were fabricated via photopolymerization using compartmental fabrication device. This device allowed fabricating computer aided designed (CAD) geometries precisely and encapsulating different cells in different hydrogel posts while building a whole geometry. The hydrogel texture characterization was performed using colored hydrogel solutions and it is observed that the device keep the distinct post in contact precisely. A brain model was created using neural, epithelial and endothelial cells as a proof of concept. Cell distribution was evaluated using cell trackers.

The viability and the proliferation assays were also performed and the viability was above 80% while a positive proliferation was observing.

Overall findings showed that this device offers a practical way to fabricate and align precisely designed three-dimensional hydrogel scaffolds which allows modelling various types of tissues and organs and it tis promising for further applications in many fields.

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DOPAMINE METABOLISM RELATED GENE EXPRESSION CHANGES IN 6-OHDA INDUCED MODEL OF PARKINSON'S DISEASE

Ekin Sonmez[1], Esra Nur Yigit[1], Isa Yuksel[2], Tunahan Cakir[2], Isil Aksan Kurnaz[1,3]

1Gebze Technical University, Institute of Biotechnology, Kocaeli, Turkey. 2Gebze Technical University, Department of Bioengineering, Kocaeli, Turkey. 3Gebze Technical University, Department of Molecular Biology and Genetics, Kocaeli, Turkey

ekinsonmez@gtu.edu.tr

Aims: Parkinson's Disease (PD) is a neurodegenerative disease, which is characterized by dopaminergic cell death in substantia nigra. Although the major symptoms are known in detail, the molecular mechanism behind the cellular death and possible survival mechanisms is not clear. Hydroxidopamine (6-OHDA) is a catecholaminergic neurotoxin that is widely used as a model of Parkinsons's Disease. In this study, we aimed to determine Parkinsonian death and survival mechanisms in terms of gene expression changes using 6-OHDA in SH-5YSY cell line model of PD.

Methods: SH-SY5Y cells were treated with 100 uM 6-OHDA and cells were collected to perform transcriptome analysis. Transcriptome analysis was performed using Agilent G3 Human Gene Expression 8x60K microarray kit. Differentially expressed genes were determined to identify shared molecular functions and cellular pathways. The data was also mapped on human protein-protein interaction network to identify significantly regulated and interacting modules. The data from microarray results and PD marker gene expression changes were validated by qPCR.

Results: The expression of marker genes for dopamine metabolism, such as Maob, Ddc, Vamp8, Adcy7 etc. were abundantly increased with 6-OHDA treatment. The qPCR results showed that the expression levels were elevated.

Conclusions: In Parkinsonian disorders, it is important to determine cellular responses at molecular level. Microarray profiling of 6-OHDA model of PD revealed dopamine metabolism related gene expression changes leading to cellular death. To be able to develop novel neuroprotective strategies, in-depth knowledge of PD-related cellular survival and death related pathway and their interplay with dopamine metabolism.

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EVALUATION OF NEURODEGENERATION INDUCTION OF TRANSWELL (CANCER-NEURON COCULTURE) CAN BE REVERSED BY MOMORDICA AND MORINGA

Fatma Yesilyurt[1], Ali Taghizadehghalehjoughi[1,2], Ahmet Hacimuftuoglu[1]

1Medical Pharmacology Department, Faculty of Medicine, Atatürk University, Erzurum, Turkey 2Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine, Ataturk University, Erzurum, Turkey

fatmayesilyurttt@gmail.com

Aims: The Transwell method is commonly used to identify and evaluate chemical cues that modulate cell migration or spread. Glioblastoma is the most common subtype of primary brain tumors in adults and is characterized by high proliferative indexes and aggressions that are thought to be the most lethal of human cancers. Cancer and neurons can grow in the same environment, but cancers have toxic effects on neurons and kill neurons. In our study, we used transwell membrane to examine this condition in more detail and we implanted the neurons into the transwell membrane. After culturing, we used moringa and momordica extracts to eliminate inflammation.

Methods: Neuronal cells were obtained from Ataturk University (Erzurum, Turkey) Dep. of Medical Pharmacology. Cancer cells were given into the cerebellum and the olfactory cells with a transwell membrane. Moringa and momordica plant extracts were added to the wells after 48 hours of treatment at 150, 200 and 250µg/mL concentrations. MTT and morphological changes were investigated after 24 hours.

Results: The results differed in cerebellum and olfactory cells. At 250µg/mL concentration of moringa and momordia, it has shown a protective effect on neurons while killing cancer cells. Neurons were conserved at 150 and 200µg/mL concentrations of both extracts, but the neuron protective effect decreased by the dose decreasement.

Conclusıons: Owolabi et al. reported that moringa extract, when taken alone, does not damaging effects in the cerebral cortex. Dileonardi AM et al. reported that momordica plays a critical role in the prevention of neuronal degeneration. This informations have a correlation with our study.

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EFFECTS OF ALOE BARBADENSIS MILLER AND METFORMIN ON GLIOBLASTOMA CELL LINES: IN VITRO MODEL

Aysegul Yilmaz[1], Ali Taghizadehghalehjoughi[2], Ahmet Hacimuftuoglu[1]

1Department of Medical Pharmacology, Faculty of Medicine, Ataturk University, Erzurum, Turkey;
2Department of Toxicology and Pharmacology. Faculty of Veterinary, Ataturk University, Erzurum, Turkey

aysegulmg@gmail.com

Objective: Studies have shown that plant leaf extracts of Aloe Barbedensis Miller have antioxidant, immunostimulant and anticancer effects. Metformin is a cheap, well-tolerated oral agent commonly used in primary care for type2 diabetes. In our study, we aimed to investigate the migration and proliferation effects on different cancer cell lines by giving these two substances, which are known to have anticancer properties, at defined doses.

Materials and Methods: Cancer cell lines were obtained from Dep. of Medical Pharmacology, Ataturk University. The plant aqueous extract was prepared in 100, 150, 200, and 250µgr/mL doses, metformin 40 and 80µgr/mL and in various combinations. Fifteen groups of U373 were administered to the HUVEC cell line with LN405 cancer cell lines. Migration, proliferation and survival rates were examined in each group. The results were analyzed by one way ANOVA method in SPSS 21.00 program.

Results: The vitality in our control group was defined as 100% and the other groups were rated accordingly. When the migration and proliferation were observed in HUVEC, the lowest activity was observed in Met 80 + Aloe 250µgr/mL group with 64% ($P < 0.001$). In addition, LN405 and U373 cancer cell lines showed the lowest activity in the Met 80 + Aloe 250µgr/mL and Met 40 + Aloe 250µgr/mL groups($P < 0.001$).

Conclusions: Qin Pan et al. reported that the aloin compound obtained from leaves of the aloe barbadensis plant with HUVEC and observed the lowest cell viability at 60 and 80µmol/L. Arcella et al. also studied the aloe-emodine (AE) compound in the U87MG cell line, a type of glioblastoma. The results showed that AE viability at 20 and 40µM doses decreased significantly. Our results have shown that we obtained low levels of cancer and vascularization with these studies.

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A FAMILY WITH EARLY-ONSET FAMILIAL ALZHEIMER DISEASE ACCOMPANIED BY GERMLINE PSEN2 MUTATIONS

Beste Yurdacan[1], Isil Ezgi Eryilmaz[2], Unal Egeli[2], Mustafa Bakar[3], Dilara Kamer Colak[2], Gulsah Cecener[2], Berrin Tunca[2]

1Ege University, Faculty of Pharmacy, Pharmacology Department, Izmir, Turkey. 2Bursa Uludag University, Faculty of Medicine, Medical Biology Department, Bursa, Turkey. 3Bursa Uludag University Faculty of Medicine, Neurology Department, Bursa, Turkey

besteyurdacan93@gmail.com; egeli@uludag.edu.tr

Aims: Early-Onset Familial Alzheimer Disease (EOFAD) is a genetic disorder that associated with autosomal dominant mutations in the disease susceptibility genes. The aim of the present study is to show that genetic analysis is a guide for risk assessment before diagnosis in family members with EOFAD.

Method: For genetic analysis, the five members of EOFAD family were transferred from Neurology to Medical Biology at Bursa Uludag University. The four of them have not been diagnosed with EOFAD yet. DNA sequence analysis of the EOFAD-related genes, PSEN1, PSEN2 and TREM2, was performed in the peripheral blood samples of these family members.

Result: The five members, including a patient undergoing mutation analysis, died from EOFAD in this family. Additionally, two variations that related with EOFAD, c.129C>T (p.Asn43=) and c.69T>C (p.Ala23=), were detected in PSEN2 gene in the members who included in genetic analysis.

Conclusions: Our study shows that genetic analysis in susceptibility genes for the members of a family with EOFAD is quite informative for risk assessment and prophylactic treatment approaches before diagnosis.

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DIAZEPAM-INDUCED LOSS OF INHIBITORY SYNAPSES MEDIATED BY PLCΔ/ CALCIUM/CALCINEURIN SIGNALLING DOWNSTREAM OF GABAA RECEPTORS

Jovanovic JN[1], Nicholson MW[1], Ali AB[1], Duchen M[2]

1UCL School of Pharmacy, University College London, London, UK;
2UCL Division of Biosciences, University College London, London,UK

j.jovanovic@ucl.ac.uk

Aims: Benzodiazepines facilitate the inhibitory actions of GABA by binding to GABAA receptors (GABAARs), ligand-gated chloride/bicarbonate channels, which are the key mediators of transmission at GABAergic synapses in the brain. The aim of this study was to characterise cellular and molecular mechanisms underlying tolerance to benzodiazepines.

Methods: Structural and functional changes in inhibitory GABAergic synapses were studied in cultured cerebrocortical neurones using immunocytochemistry, live cell confocal imaging and electrophysiology. GABAA receptor trafficking and cell surface expression were studied using cell surface ELISA, immunoblotting and immunoprecipitation.

Results: We report that prolonged exposure to diazepam, the most widely used benzodiazepine in clinic, led to a gradual breakdown of GABAergic synapses. The loss of synapses and the preceding, time- and dose-dependent decrease in surface levels of GABAARs, mediated by dynamin-dependent internalisation, were blocked by Ro 15-1788, a competitive benzodiazepine antagonist, and bicuculline, a competitive GABA antagonist, indicating that prolonged enhancement of GABAAR activity by diazepam is integral to the underlying molecular mechanism. Characterisation of this mechanism revealed a metabotropic-type signalling downstream of GABAARs, involving mobilisation of intracellular Calcium and activation of the Calcium/Calmodulin-dependent phosphatase Calcineurin, which promotes their endocytosis. Functional coupling between GABAARs and Calcium stores was sensitive to Phospholipase C (PLC) inhibition, and regulated by PLCδ, a PLC isoform found in direct association with GABAARs.

Conclusion: This newly discovered PLCδ/Calcium/Calcineurin signalling pathway converts the initial enhancement of GABAARs by benzodiazepines to a long-term downregulation of GABAergic synapses, potentially underpinning the development of pharmacological and behavioural tolerance to these widely prescribed drugs.

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DISCOVERY OF SMALL MOLECULE ACTIVATORS OF MITOPHAGY TO TREAT NEURODEGENERATIVE DISEASES

Heather Weir, Gregory A O'Sullivan
Astex Pharmaceuticals, Cambridge, United Kingdom

heather.weir@astx.com

Aims: Mitochondrial dysfunction is a common feature of many neurodegenerative diseases and is a driver of the underlying pathology. Selective removal of damaged mitochondria via mitophagy can protect cells from further damage, and enhancing this process is thought to hold therapeutic potential. To enable identification of mitophagy activators, we have developed a cell-based high content imaging assay that measures mitophagy induction.

Methods: We engineered human neuroglioma cells to express a pH-sensitive fluorescent reporter, which monitors the delivery of damaged mitochondria to lysosomes and thus serves as a readout of mitophagy induction. Using high content imaging and automated analysis, the number of mitophagosomes can be accurately quantified in a robust, unbiased manner.

Results: As a proof of principle, cells were treated with the iron chelator deferiprone (DFP), previously reported to induce mitophagy. DFP increased the number of mitophagosomes per cell in a dose-dependent manner, demonstrating the utility of this assay in detecting activators of mitophagy.

Conclusions: In summary, we have generated a high throughput platform with which to identify small molecule mitophagy modulators, which have the potential to be developed into novel treatments for neurodegeneration.

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INHIBITION OF PROTEASE-ACTIVATED RECEPTOR 1 AMELIORATES BEHAVIORAL DEFICITS AND RESTORES HIPPOCAMPAL SYNAPTIC PLASTICITY IN A RAT MODEL OF STATUS EPILEPTICUS

A. Savotchenko[1], M. Semenikhina[1], R. Bogovyk[1], M. Fedoriuk[1], O. Nikolaienko[1], Lina T. AlKury[2], O. Krishtal [1],E. Isaeva[1]

1Bogomoletz Institute of Physiology, Kyiv, Ukraine. 2College of Natural and Health Sciences, Zayed University, Abu Dhabi, United Arab Emirates

savrasova10@gmail.com

Brain injuries are often accompanied by the disruption of blood-brain barrier (BBB) integrity. Consequences of BBB dysfunction can greatly affect neuronal excitability and induce epileptic seizures. Inhibition of protease-activated receptor 1 (PAR1), a major thrombin receptor in the brain, produces an anti-epileptogenic and neuroprotective effects in an experimental model of temporal lobe epilepsy (TLE). Since serine proteases and PAR1 are implicated in the synaptic plasticity and memory formation, the aim of the present study was to evaluate the involvement of PAR1 in synaptic plasticity and behavior deficits following SE.

Using lithium-pilocarpine model of TLE in juvenile rat, we demonstrate that inhibition of PAR1 rescues SE-induced synaptic plasticity deficits in CA1 region of hippocampus.

Although treatment with PAR1 antagonist does not ameliorate spatial learning deficits, it attenuates an anxiolytic-like behavior in juvenile rats after SE.

Taken together; our data suggest an important role of PAR1 in SE-induced synaptic and behavioral alterations and provide a new insight into the cellular mechanisms underlying behavioral impairments associated with epilepsy.

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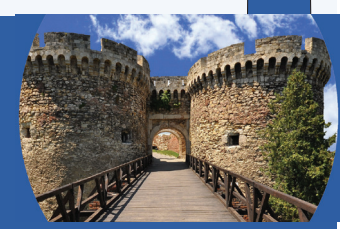

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TELOMERASE-DEPENDENT SENESCENCE AND INFLAMMATION WITH AGEING IN THE ZEBRAFISH BRAIN

Raquel R. Martins[1,2], Pam Ellis[1,2], Nadiyah Mughal[1,2], Ilaria Bellantuono[1,3] and Catarina Henriques[1,2]

1 Department of Oncology and Metabolism, Medical School, The University of Sheffield, Sheffield, UK;
2 Bateson Centre, University of Sheffield, Sheffield, UK;
3 MRC-Arthritis Research UK Centre for Integrated Research into Musculoskeletal Ageing-CIMA, Liverpool, United Kingdom

rrmartins1@sheffield.ac.uk

In humans, limited telomerase expression leads to telomere shortening and consequent replicative senescence. In turn, senescent cells, via secretion of inflammatory factors known as Senescence-Associated Secretory Phenotype (SASP), are thought to contribute to inflammation. Importantly, both telomere shortening, decreased expression of telomerase and senescence-associated markers have been associated with neurodegenerative diseases. However, whether increased senescence in the aged brain is caused by limited telomerase expression and/or telomere dysfunction and whether these drive neuro-inflammation, remains unclear. We hypothesize that telomerase restriction with ageing leads to an accumulation of senescent cells and associated inflammation in the brain.

To test this, we used zebrafish as an ageing model, which, like in humans, telomere shortening is a key driver of cellular senescence and associated inflammation. Using a combination of immunofluorescence, enzymatic assays and RNA Sequencing techniques, our work shows that the zebrafish brain displays increased senescence and inflammation with ageing. These are anticipated in the absence of telomerase (tert-/-), suggesting to be telomerase dependent.

Importantly, our data suggest that increased inflammation correlates with increased blood-brain barrier permeability and with macrophages infiltration from the periphery. Remarkably, telomerase-dependent accumulation of senescence in the brain occurs not only in the expected proliferative areas but also in non-proliferative ones, where it is unlikely due to telomere-dependent replicative exhaustion. Together, our work suggests that telomerase has a protective role against the accumulation of senescence and neuro-inflammation with ageing, possibly via its non-canonical, telomere-independent functions.

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POSTER SESSION 2

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IBA1+ MICROGLIA COLOCALIZE WITH HOMER1+ SYNAPSES AND REVEAL TWO NOVEL SUB-TYPES OF GABAERGIC NEURON IN GUINEA PIG INFERIOR COLLICULUS

S. D. Webb, L.D. Orton

School of Healthcare Science, Manchester Metropolitan University, Manchester, United Kingdom

samuel.webb@stu.mmu.ac.uk

Aims: Inhibition is essential for auditory processing. The inferior colliculi (IC), principal nuclei in the auditory system, contain around 30% GABAergic neurones. Microglia have been shown to interact with neurones during ongoing processing. We sought to use functional differences between sub-nuclei in IC, to investigate microglia-neuron interactions.

Methods: Confocal imaging of fluorescent immunohistochemistry (GAD67, Iba1, GFAP, synaptophysin, homer1) in 60µm coronal sections of young adult, guinea pigs (n=4) was performed. Synaptic and cellular labelling was semi-quantified (ImageJ) and statistical tests were performed (Prism & SPSS).

Results: We found a high density of GAD67+ neurones in central nucleus (predominant afferent drive ascending from brainstem, high frequency, sharp tuning, limited synaptic plasticity) with significantly fewer neurones in dorsal cortex (predominant afferent drive from cortex or contralateral IC, low frequency, broad tuning, strong synaptic plasticity). Numerous Iba1+ processes abutted GAD67+ somata in all sub-regions. Iba1+ microglia were more ramified in dorsal cortex, with more branching points and shorter distances between branches. GAD67+ neurons (40 per sub-region) were described by two clusters. ROC analyses revealed clusters could be discriminated based on total Iba1+ contacts abutting GAD67+ somata. 3D reconstruction and colocalisation of Iba1 with synaptic markers revealed greatest numbers in dorsal cortex. Puncta were located on primary, secondary, tertiary and quaternary Iba1+ ramifications across sub-regions.

Conclusions: Iba1+ microglia in IC have varied morphological characteristics related to sub-region dependent inhibitory processing. Colocalisation of Iba1+ processes at excitatory synapses in dorsal cortex suggests a role for microglia in ongoing synaptic function and plasticity in IC.

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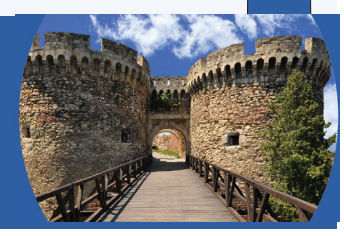

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A VALIDATED GCAMP VIRAL METHOD FOR MICROENDOSCOPIC IMAGING IN RAT HIPPOCAMPUS CA1 DURING ACTIVE BEHAVIOR

Jonathan Zapata, Srishti Gulati, David Cheng, Jonathan Nassi, Alice Stamatakis

Inscopix Inc. Palo Alto, CA, United States

jzapata@inscopix.com

Aims: A large part of our understanding of the neurophysiological basis of sleep, memory, motivation and addiction has been derived from rodent experiments, particularly those involving rats. Studying behavior precisely paired with in-vivo cell specific neurological recordings is essential in deciphering how certain regions of the brain are involved in these behavioral attributes.

Methods: One such tool that is extensively used to gather such information utilizes genetically encoded calcium indicators in combination with cell-specific viral-mediated delivery and one-photon imaging in freely behaving animals.

Results: Here we demonstrate an end-to-end solution to obtain stable miniaturized microscope (nVista3, Inscopix Inc.) neural recordings from hundreds of pyramidal neurons in rat CA1 region of hippocampus utilizing pre-diluted and validated ready-to-inject virus and an active behavior responsive commutator for efficient behavioral testing.

Conclusions: These solutions will enable researchers to link behaviors to patterns of activity in the rat brain which will in turn lead to cutting-edge discoveries in neurophysiology and systems neuroscience.

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POSTER SESSION 2

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PROGNOSTIC ASSESSMENT OF APOLIPOPROTEIN E ALLELE INFLUENCE ON COGNITIVE OUTCOME AFTER TRAUMATIC BRAIN INJURY

Zoltán Apa[1], Stefan Strilciuc[2], Nicoleta Jemna[2], Livia Popa, [2], Ioana Muresanu[2], Olivia Verisezan Rosu[2], Dafin F. Muresanu[3],[4],[5],[6],[7],

[1]Teachers College Columbia University/ Roneuro Institute for Neurological Research and Diagnostic.
[2]Roneuro Institute for Neurological Research and Diagnostic.
[3]President of the European Federation of NeuroRehabilitation Societies (EFNR).
[4]Professor of Neurology, Chairman Department of Neurosciences.
[5]"Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania.
[6]Chairman "RoNeuro" Institute for Neurological Research and Diagnostic.
[7]President of the Society for the Study of Neuroprotection and Neuroplasticity (SSNN)

za2149@tc.columbia.edu

Traumatic Brain Injury (TBI) is considered a possible risk factor for development of late-life dementia. The link between TBI and dementia development is inconclusive throughout the literature. We explored the association between TBI and dementia development cascade to investigate whether the severity of injury and Apolipoprotein E allele presence is associated with outcome and cognitive functions in TBI.

We performed secondary data analysis on TBI patients from a single-center clinical trial. ApoE determination at baseline and neurocognitive outcomes measured at 10, 30 and 90 days were included in a multiple linear regression model to determine the predictive value of ApoE on TBI outcome scales, controlling for severity of the injury, age, and gender.

A total of 142 patients aged 19-79 with a diagnosis of TBI were included in multiple linear regression models. A strong association was observed between ApoE and Baseline Prognostic Mortality Risk Score. No significant ApoE prediction value was observed for Hospital Anxiety Depression Scale (30, 90 days), Stroop Color-Word Test, Digit Span (30, 90 days) and Processing Speed Index (10, 30, 90 days). Two significant regression equations were found for ApoE as a predictor of Mini-Mental State Examination at days 10 and 30.

ApoE might not be associated with cognitive decline and dementia development when controlled for TBI severity in a single-dimensional approach. Evidence of the APOE effect on recovery after TBI remains unknown. Multidimensional analysis of long-term cognitive impact and risk of dementia development in the face of incident TBI is warranted.

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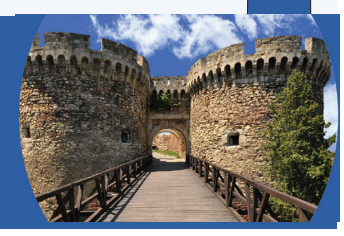

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POSTER SESSION 3

P324

EXPLORING THE ROLE OF PREFRONTAL CORTEX NICOTINIC RECEPTORS ON COCAINE-ASSOCIATED MEMORY

Verónica Pastor[1,2], Fernando Castillo Díaz[1], Valeria C. Sanabria[1], Jorge H. Medina[1], Marta C. Antonelli[1]

1CONICET-Universidad de Buenos Aires, Instituto de Biología Celular y Neurociencia "Prof. E. De Robertis" (IBCN), Buenos Aires, Argentina.
2Universidad de Buenos Aires, Facultad de Medicina, Departamento de Ciencias Fisiológicas, Buenos Aires, Argentina.

verpastor@fmed.uba.ar

Nicotinic acetylcholine receptors (nAChRs) in the prefrontal cortex (PFC) have critical roles in cognitive function including attention and memory and are key players in plasticity processes. Recently, it has been shown that glutamatergic neurons in the PFC mediate the formation of cocaine-associated memories. However, the potential role of nAChRs on that mechanism is still unexplored. Aims: This study was design to assess whether alpha 7 nAChRs in the PFC are required for the formation of cocaine-associated memories and the underlying molecular mechanisms.

Methods: Cocaine-associated memory was assessed by using conditioning place preference (CPP), where rats where trained to associate the rewarding effects of cocaine (20 mg/kg) with the environmental context in which it was received. We used behavioral pharmacology to study the effect of intra-PFC methyllycaconitine, a specific antagonist of the α7 subtype of nAChRs, on the acquisition of cocaine-induced CPP in adult rats.

Results: We found that pharmacologic inhibition of α7 nAChRs in the PFC before conditioning impaired a 4-trial cocaine-induced CPP without altering acute locomotor response. We are now exploring the expression of molecular substrates for cocaine-associated memory on the mesolimbic circuit to shed light on signaling pathways related to our behavioral findings.

Conclusions: Our results suggest that α7 nAChRs in the PFC participate in the acquisition of cocaine CPP. Considering that drug seeking often depends on the association between drug-paired cues and the rewarding effects of the drug, α7 nAChRs in PFC could be considered as potential targets for the prevention of addictive behaviors.

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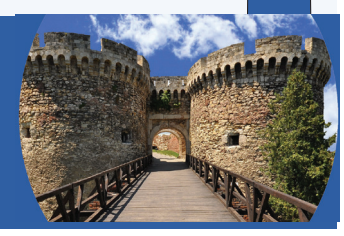

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FUNCTIONAL NEUROANATOMY OF PRODYNORPHIN

Iwona Kmiec[1], Mario Mietzsch[2], Luca Zangrandi[1], Lill Andersen[3], Thomas Rülicke[3], Gerald Zernig[4], Regine Heilbronn[2], Christoph Schwarzer[1]

1Department of Pharmacology, Innsbruck Medical University, Austria, 2Institute of Virology, Charité - Medical University Berlin, Germany, 3Institute of Laboratory Animal Science, University of Veterinary Medicine, Vienna, Austria, 4Experimental Psychiatry Unit, Department of Psychiatry 1, Medical University of Innsbruck

iwona.kmiec@i-med.ac.at

Aims: DYN and KOPr are abundantly expressed throughout limbic brain areas and were shown to be involved in stress-induced behavioural alterations, including increased aversion, dysphoria, and anxiety. In line with this, the DYN/KOPr system is implicated in the pathophysiology of depression and addiction. Understanding the highly complex organization of the DYN/KOPr system is a prerequisite for potential therapeutic intervention.

Methods: To gain deeper insight into the functional neuroanatomy of the DYN/KOPr system, we implemented independent, yet complementary strategies based on restricted PDYN knock-out or PDYN re-expression within the extended amygdala. Such mice were tested in paradigms related to anxiety and stress-coping behaviour and cocaine-induced conditioned place preference.

Results: Stress-induced reinstatement of the conditioned place-preference was observed in wild-type animals and several control groups. By contrast, no reinstatement was observed in animals deficient for PDYN expressed in the central amygdala, the bed nucleus of the stria terminalis or NKB-expressing neurons. Still these animals re-expressed place preference upon cocaine challenge. Interestingly, no differences in trait anxiety or stress coping behaviour was observed applying standard tests.

Conclusions: Our findings suggest critical involvement of specific populations of dynorphinergic neurons in stress-induced relapse of drug abuse.

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MULTIPLEXING MOTOR FUNCTIONS AND IMPULSIVE TRAITS IS MOLECULARLY DISSOCIATED BY SUBTHALAMIC METABOTROPIC GLUTAMATE RECEPTOR 4

Lukasz Piszczek[1], Andreea Constantinescu[1], Anton Pekcec[2], Janet Nicholson[2] and Wulf Haubensak[1]

1IMP- Insitiute of Molecular Pathology, Campus Vienna-Biocenter 1, Vienna. 2Boehringer-Igelheim, Biberach, Germany

andreea.constantinescu@imp.ac.at

Aims: Inhibitory control, the ability to suppress and cancel prepotent responses is a key element of cognitive control. Its impairment underlies both impulsive and compulsive behaviours, which are symptoms of conditions such as: ADHD and OCD. Despite its ethological and clinical significance, neuronal mechanisms specifically controlling impulsive responding remained largely unknown. Using a well-established impulsivity behavioral task combined with functional imaging, and a set of brain-region specific manipulations, we screened for brain regions and molecular targets that can dissociate trait impulsivity from general motor control.

Methods: We combined the Go/No-Go task (GNG) with functional imaging (fMRI) to identify brain regions linked to impulsivity. Next, we conducted a set of optogenetic and pharmacological experiments along with RNA silencing in order to identify brain regions modulating trait impulsivity and to pinpoint a potential molecular target.

Results: This screen identified the subthalamic nucleus (STN), a relatively small node of the basal ganglia circuitry primarily linked to general motor control. Its optogenetic inhibition in GNG task increased impulsivity. Similarly, administering a positive allosteric modulator of the metabotropic glutamate receptor 4 (mGluR4), a molecule thought to decrease STN firing, mimicked previous optogenetic inhibition phenotype. Conversely, shRNAi mediated knocking down of STN mGluR4 reduced impulsivity. Importantly, our manipulation did not affect general motor behavior.

Conclusions: Taken together, our study suggests that STN circuitry is involved in both motor and impulsive inhibition and this function is dissociated at the molecular level by the mGluR4, a novel biomedical target at the intersection of motor and cognitive functions.

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DATA DRIVEN EXPLORATION OF MOUSE BEHAVIOR IN THE GONO-GO TASK

Lukasz Piszczek[1], Manuel Pasieka[2,3], Andreea Constantinescu[1,3], Wulf Haubensak[1]
1IMP - Research Institute of Molecular Pathology, Vienna, Austria. 2Vienna Biocenter Core Facilities, Vienna, Austria. 3Equal contribution

lukasz.piszczek@imp.ac.at

Aims: Executing behaviors are contingent on environmental settings, for instance conditionally withholding stereotypic responses in time. Impulsivity, the underlying multifaceted trait, is a key feature of cognitive control, linked to incentive salience, attention and the ability to suppress and/or cancel prepotent responses. In our study we have used the symmetrical Go/No-Go task (GNG) as a model for behavioral inhibition to provide a deeper understanding of evolution of behavioral states in an impulsivity-related setting.

Methods: Here we combined the GNG task, with a machine learning approach to investigate animal behavioral strategies in the task. We have determined mouse behavioral states in a data-driven fashion, using unsupervised clustering algorithms benchmarking the results on data set from high/low impulsive, trained animals. Finally, we have investigated how these parameters are affected by pharmacological manipulation using compounds known to affect impulsivity in both rodents and humans.

Results: We have successfully developed a machine learning pipeline to combine sensor data with video analysis into behaviour states. Analysis of high and low impulsive animals show different temporal behavioral profile and shifts within these states that are more complex than a simple mirror image as would be expected when looking at classical measures alone. Similarly comparing this natural split and pharmacology revealed use of divergent strategies in animals having comparable impulsivity levels as measured by classical measures.

Conclusions: Our preliminary data suggest that this analysis detects drug induced changes in behavioral patterns and strategies in animal behaviour that go beyond the classically investigated parameters.

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EFFECTS OF SOCIAL ISOLATION ON SOCIAL INTERACTION BEHAVIOR AND ULTRASONIC VOCALIZATIONS IN ADULT FEMALE MICE.

Van der Jeugd A, Kempen B, Lena Hofbauer, Victoria Salazar, Inne Seeuws, Rudi D'Hooge
Laboratory for Biological Psychology, Brain and Cognition, Faculty of Psychology and Educational Sciences, KU Leuven, Leuven, Belgium
ann.vanderjeugd@kuleuven.be

Social isolation and loneliness are associated with selectively altered cognitive and affective processes in humans and other mammals, but the mechanisms underlying these deficits remain largely unexplored.

We present here evidence that when adult mice are chronically isolated, they produce social memory deficits and distinct alterations in their ultrasonic vocalization (USV) calling repertoire, a finding that could be rescued by intense social stimulation. We isolated a group of 6 month old female WT mice for 1 month (n=10), control mice were group-housed (n=10). Next, we performed tests of sociability and social memory with USV recording. After these tests, our isolated mice underwent a nonpharmacological intervention: one month of re-socialization, again followed by USV testing.

Isolated mice performed worse on a social memory test compared to our grouphoused social mice using the Social Preference / Social Novelty (SPSN) test. Isolated animals did emit USVs, this is in line with the sociability results in the SPSN test where they also explored the stranger mice intensely (comparable to group-housed control mice). However call repertoire of isolated mice was limited, and this could be rescued by re-socialization treatment. After one month of treatment, the posttreatment USVs of the same mice now displayed more complex and frequency jump calls compared pre-treatment.

Hence, measuring USV emissions is an useful tool in studying the mechanisms that underlie the emotional disturbances featuring certain psychological conditions, as well as in the development of suited non-pharmacological therapies.

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DNA METHYLATION CHANGES OF NMDA RECEPTOR IN RATS AFTER POST-WEANING SOCIAL ISOLATION

Loureiro, C. M.[1,2]; Fachim, H. A.[3]; Corsi-Zuelli, F.[4]; Shuhama, R.[4] Joca, S. R. L.[5]; Menezes, P. R.[6]; Dalton, C. F.[2]; Del-Ben, C. M.[4]; Louzada-Junior, P.[1]; Reynolds, G. P.[2]

1 Internal Medicine Department, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil.. 2 Biomolecular Sciences Research Centre, Sheffield Hallam University, United Kingdom.. 3 Department of Endocrinology and Metabolism, Salford Royal Foundation Trust, Salford, United Kingdom.. 4 Neuroscience and Behaviour Department, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil.. 5 Department of Physics and Chemistry, School of Pharmaceutical Sciences, University of São Paulo, Ribeirão Preto, Brazil. . 6 Department of Preventive Medicine, Faculty of Medicine, University of São Paulo, Brazil.

camila.loureiro@usp.br; c.m.loureiro@shu.ac.uk

Background: N-methyl-d-aspartate receptor (NMDAR) subunits have been identified as candidate genes for psychiatric disorders. Evidence has also demonstrated that NMDAR epigenetic changes may be responsible for deficiencies in excitatory neurotransmission, suggesting its role in the neurobiology of psychosis. Aims: As we found altered NR1 and NR2 protein/mRNA levels in rats reared in isolation in brain tissue and peripheral blood, we hypothesised that the DNA methylation changes in the promoter region of the genes Grin1 and Grin2b may underlie these changes. We also verified if these alterations are tissue specific or if the changes found in the brain extend to the blood.

Methods: In an environmental animal model of schizophrenia, male Wistar rats were kept isolated (n=10) or grouped (n=10) from weaning for 10 weeks. After this period the animals underwent an open field test and soon afterwards they were sacrificed. We analysed DNA methylation of promoter sequences of NMDAR genes in the blood and target brain areas by pyrosequencing. Non-parametric with a Bonferroni correction was used for statistical analysis and Spearman correlational analyses were carried out.

Results: Isolated-reared rats presented increased methylation of Grin1 CpG4 (p=0.038) in the prefrontal cortex and at CpG5 in the blood (p=0.045) and increased methylation of Grin2b CpG4 in blood and hippocampus when compared to grouped (p=0.047; p=0.016).

Conclusions: This study supports our hypothesis that the NMDAR changes found in the brain could also be found in blood samples. Therefore, isolation rearing produced DNA changes, highlighting the importance of the environmental influence during the development.

Funding: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP: 2012/05178-0; 2013/08216-2) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) - Finance Code 001.

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THE COMPETITIVE NMDA RECEPTOR ANTAGONIST CPP IMPAIRS SENSORY INTEGRATION, BUT NOT OLFACTORY ODDITY DETECTION, IN MALE RATS

Thaísa M. Sandini, Wendie N. Marks, Yuanyi Song, Nimra B. Tahir, John G. Howland

Department of Anatomy, Physiology, and Pharmacology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada.

thaisasandini@gmail.com

Aims: Sensory integration (SI) is a process whereby the brain uses unimodal or multimodal sensory features to create a comprehensive representation of the environment. Understanding the neurobiological mechanisms underlying SI will be useful in identifying targets for novel pharmacological approaches for treating patients with deficits in this process. Given its importance for some aspects of sensory processing, we tested whether the glutamatergic system, and NMDA receptors in particular, is involved in SI using oddity tasks requiring or not requiring SI.

Methods: We evaluated the effects of acute CPP administration in male rats. Vehicle (Saline) or CPP (10 mg/kg) were injected (i.p.) into rats 30 min before being tested on oddity tasks involving exploration of five objects. The objects differed in either one or two visual or olfactory dimensions and were arranged such that one object was unique or 'odd' whereas the other four objects were arranged in pairs. Rats were allowed to freely explore the objects for 5 minutes after which object exploration was quantified using an oddity preference (OP) score, where OP = time spent exploring odd object/total object exploration. Significant differences from chance performance were determined using one-sample t-tests.

Results: Systemic CPP treatment impaired visual (0.17±0.01 - Saline 0.28±0.01; $p<0.001$) and olfactory (0.20±0.02 - Saline 0.30±0.02; $p<0.05$) SI tasks, oddity visual task (0.19±0.02 - Saline 0.25±0.01; $p<0.05$), without affecting performance of the olfactory oddity task ($p>0.05$).

Conclusion: The present results demonstrate that NMDA receptors are critical for SI and visual oddity task but not olfactory oddity preference.

Acknowledgments/Funding Sources: CIHR, NSERC and SHRF

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DISRUPTION IN MEMORY PROCESS MEDIATES ALTERATIONS IN THE INTERVAL TIMING BEHAVIOR IN 5XFAD MICE

Richard Brown[1], Ezgi Gür[2], Emre Fertan[1], Kindree Alkins[1], Aimée A. Wong[1] & Fuat Balcı[2]

[1]Dalhousie University, Department of Psychology and Neuroscience, Halifax, Canada. [2]Koç University, Department of Psychology, Timing and Decision Making Laboratory & Research Center for Translational Medicine, Istanbul, Turkey

rebrown@dal.ca

Aims: Interval timing ability is disrupted in Alzheimer's Disease (AD) patients; however, the information-processing basis of this phenotype is not well-understood. Animal models would be beneficial for studying this behavioural phenotype, but most research on cognitive processes in transgenic mouse models of AD has focused primarily on learning and memory. The current work studies information processing in female 5xFAD mice by investigating their interval timing behavior.

Methods: Female 5xFAD (n = 10) and wild type (n = 7) mice were tested at 9 months of age in the peak interval procedure with a 15s target interval. Acquisition of timed responses throughout the experiment and timing performance at the steady state were compared between genotypes.

Results: Although both 5XFAD and WT mice exhibited acquisition of temporal control, the time of maximum reward expectancy was earlier in 5xFAD mice than the wild types. No other major timing indices differed between the genotypes.

Conclusions: The observed leftward shift in the time of maximum reward expectancy of 5xFAD mice suggests an interval timing deficit which can be explained by the altered consolidation of temporal memories. In the light of the effect of hippocampal lesion studies on timing behavior reported in earlier work and the fact that hippocampal synaptic dysfunction is seen around 6 months of age in 5xFAD mice, we suggest that observed memory consolidation-mediated interval timing phenotype in 5xFAD mice might be due to the altered hippocampal function.

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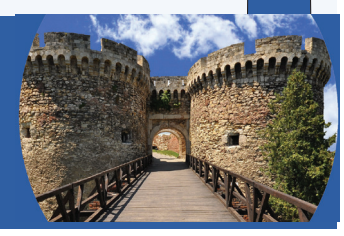

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P332

NEUROCHEMICAL CORRELATES OF COMPETITIVE EXCLUSION IN REPTILES: THE ROLE OF DOPAMINE IN THE BRAINS OF TWO SPECIES OF LIZARD - PODARCIS SICULUS AND PODARCIS MELISELLENSIS

Sofia Ana Blažević, Marko Glogoški, Barbara Nikolić, Mirta Tkalec, Dubravka Hranilović, Duje Lisičić

Department of Biology, University of Zagreb, Faculty of Science, Zagreb, Croatia

blazevic@biol.pmf.hr

In the Eastern Adriatic, the Italian wall lizard (Podarcis siculus, PS), a dominant competitor, excludes from a shared habitat the endemic Dalmatian wall lizard (P. melisellensis, PM). Brain monoamines have a wide implication in social behavior traits and could lie at the basis of this behavioral interference.

Animals of both species were collected from the same area and, after a period of acclimatization at the Department of Animal Physiology, we conducted two basic cognitive behavioral tests: open field and radial maze. In addition, we developed a high performance liquid chromatography (UV/VIS detection) method with which we reliably measured concentrations of 5HT, DA, and NA in 32 brains of the two lizard species.

In behavioral tests, PS showed significantly higher exploratory tendencies and greater activity than PM (spent more time on hind legs, entered into more radial maze arms, reached the end of an arm more frequently, moved over greater distance). In the brain, no statistically significant influence of species, sex, or their interaction was observed for NA and 5HT concentrations. PS had statistically significant higher levels of dopamine in brain, twice as much, than PM.

Taking into account that a significant aggressive relationship, with PS dominating over PM, has been previously observed, and that dopamine – linked to higher activity and initiative – directly influences this behavior, the observed differences in dopamine levels could represent a trait in these species and may contribute to the competitive exclusion of P. melisellensis by P. siculus in the Eastern Adriatic.

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P333

CONSEQUENCES OF NEONATAL NORMOBARIC HYPOXIA ON RAT BEHAVIOR

Barbara Nikolić[1], Sara Trnski[2], Matea Krizman[1], Nataša Jovanov Milošević[2], Dubravka Hranilović[1]

1University of Zagreb, Faculty of Science, Department of Biology;
2Croatian Institute for Brain Research, University of Zagreb, School of Medicine;
Zagreb, Croatia

barbara.nikolic@biol.pmf.hr

Prenatal hypoxia is one of the main causes of neonatal hypoxic-ischemic encelopathy which can result in a wide range of consequences, from mental retardation, cerebral palsy, and epilepsy to learning difficulties and behavioral disorders. Studies on rat models are necessary for understanding the behavioral outcomes of hypoxic brain injuries of different intensities, and their molecular basis.

Our research group is trying to develop a non-invasive model of rat neonatal hypoxia, which corresponds to human prenatal hypoxia. The aim of this study was to determine possible changes in locomotion, learning, anxiety-like, exploratory and social behavior in young rats neonatally exposed to normobaric hypoxia.

On the first postnatal day (PND1), 12 experimental pups were kept under normobaric hypoxic conditions (8% O2), and 12 control pups under normoxic conditions, for 2h. From PND33 to PND45 rats underwent the battery of behavioral tests: open field, hole-board, T-maze and social choice.

The level of locomotion in an open field, as well as anxiety-like and exploratory behaviors in a hole-board did not differ between the groups. Compared to the control group, the hypoxia-exposed group had a significantly smaller number of correct choices in a T-maze. In addition, males from the experimental group displayed significantly prolonged research time of the conspecific in a social choice test.

The findings suggest that the exposure of neonatal rats to hypoxia reduces the ability of spatial learning and increases the sociability in males.

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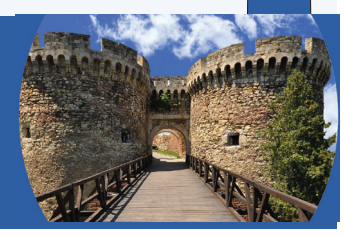

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DIFFERENCES IN MONOAMINERGIC PROFILE ACCOMPANY DIFFERENCES IN PREDATOR-INDUCED STRESS BEHAVIOR BETWEEN MAINLAND AND ISLAND POPULATIONS OF LIZARD PODARCIS SICULUS

Dubravka Hranilović[1], Sofia Ana Blažević[1], Barbara Nikolić[1], Marko Glogoški[1], Diana Hews[2], Duje Lisičić[1]

1 Department of Biology, University of Zagreb, Faculty of Science, Zagreb, Croatia;
2Indiana State University, Terre Haute, Indiana, USA.

blazevic@biol.pmf.hr

Italian wall lizard (Podarcis siculus) occupies a variety of habitats, including eastern Adriatic coast with surrounding islands, and undergoes population specific adaptations in morphology, physiology and behavior. By using mainland (ML) and island (ISL) populations of this highly adaptable lizard species, we have been investigating to what extent does different ecological context, in which two populations of the same species reside, shape adaptive behavior and affect its neurochemical make-up.

In this study, in situ escape behavior was examined in 41 ML and 39 ISL adult male lizards by measuring distance at which an animal initiates flight at the approach of an observer, distance to which they flee, and time spent in a hiding place. An additional ten individuals were collected from each location and brought to laboratory where, after a period of acclimation, whole-brain concentrations of serotonin (5-HT), dopamine (DA), noradrenaline (NA) and adrenaline (ADR) were determined by ELISAs.

While ML and ISL population displayed no significant difference in flight initiation distance or in flight distance, ML lizards remained significantly longer in a hiding place. Brains from ML lizards displayed significantly higher concentrations of NA and ADR, but not of 5-HT and DA levels, compared to those of ISL lizards.

Our results indicate higher level of predator-induced stress in ML population, as well as higher brain concentrations of neurotransmitters mediating response to stress, suggesting that monoaminergic profile might represent one of the mechanisms through which the environment shapes adaptive behavior.

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ADAPTATION OF MISMATCH NEGATIVITY LIKE POTENTIAL – TIME DURATION AUDITORY STIMULI IN ROVING PARADIGM

Vajčner A[1,2], Minks E[1]

1First Department of Neurology, Faculty of Medicine, Masaryk University and St. Anne's Hospital, Brno, Czech Republic. 2Department of Sport Medicine and Rehabilitation, Faculty of Medicine, Masaryk University and St. Anne's Hospital, Brno, Czech Republic

vajcneradam@gmail.com

Mismatch negativity is the component of event-related potentials, which is generated even in the absence of attention. It is the electrophysiological marker of automatic detecting sensory information processing. Stimulus-specific adaptation is the reduction in the responses to a common sound relative to the sound when rare. It was originally described in the primary auditory cortex as the neuronal correlate of the mismatch negativity.

The aim of this study is to find out other structures involved in Mismatch negativity – like potential. And analyse adaptation processing of the auditory deviant stimuli in insula anterior and posterior.

We included 14 patients (age 27 ± 7) with Epilepsy with intracerebral electrodes in neurosurgery program. 12 patients were implanted electrodes in insula anterior and 8 of them were implanted in insula posterior. We used auditory roving paradigm. We analysed 3 periods of the recording and compared each other to find out adaptation through the EEG data (100-300 ms after the deviant stimuli).

We found Mismatch Negativity-like potentials (100-250 ms latency) in insula anterior (11 patients) and insula posterior (8 patients). The results suggest differences of eliciting mismatch negativity potential during time. Differences were found between anterior and posterior insula. Eliciting of MMN-like potential is different at the beginning, middle and the end of roving paradigm.

The study has limitations but it seems, that adaptation of auditory Mismatch Negativity is not so specific process that we suggest.

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ANIMAL MODEL OF SCHIZOPHRENIA INDUCED BY DIZOCIPLINE (MK-801): SPATIAL AND TEMPORAL DISRUPTIONS ON ROTATING ARENA

Kristyna Maleninska [1,2,3], Pavla Jandourkova [1,2], Tereza Nekovarova [1,2,3,4], Ales Stuchlik [1]

1 Institute of Physiology, Czech Academy of Sciences, Prague, Czech Republic. 2 Faculty of Science, Charles University, Prague, Czech Republic. 3 National Institute of Mental Health, Klecany, Czech Republic. 4 Third Faculty of Medicine, Charles University, Prague, Czech Republic

kristyna.maleninska@fgu.cas.cz

Aims: In this task, we tested temporal and spatial strategies in rat model of psychosis induced by dizocilpine. We predicted that under specific doses, spatial strategy should not be disrupted but timing strategy should be affected. Aim of this experiment is demonstration of temporal disruption in animal model of schizophrenia.

Methods: For this experiment we used modified active place avoidance task on rotating arena (Carousel) which tests spatial and temporal cognition. This task is based on stable room-frame to-be-avoided sector on rotating arena. The experiment lasted five weeks with daily 20-min sessions. After the training we applied dizocilpine and observed changes in performance. We tested male Long-Evans rats from at the age of four months.

Results: Carefully-titrated doses of dizocilpine disrupted timing strategy but not performance based on spatial orientation. Rats were not able to avoid the aversive sector in parts testing timing strategies and had higher number of entrances into it.

Conclusions: The application of dizocilpine induced changes which we expected. The neural circuit which is affected in patients with schizophrenia is the same which should be the main in interval timing and our results support this concept. This modified task can serve as a useful tool for testing other animal models.

This work was supported by GACR grants 17-04047S, 19-03016S and AZV grant 17-30833A. It was also supported by Academic CZ-PL bilateral mobility project PAN-17-07, ERDF project, OPPK Microscopic System CZ.2.16/3.1.00/28034, ERDF OPPK BrainView CZ.2.16/3.1.00/21544 and MEYS (LM2015062) Czech-BioImaging and by H2020 INFRADEV-01-2017 project ID-EPTRI (Grant Agreement 777554).

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DEVELOPMENT AND OPTIMALIZATION OF THE NOVEL ONE–TRIAL LEARNING TASK

Dominika Radostová [1,2], Hana Brozka [1], Adela Pistikova [1], Karel Vales [1,3], Ales Stuchlik [1]

1Institute of Physiology of the Czech Academy of Sciences, Prague, Czech Republic. 2Second Faculty of Medicine, Charles University, Prague, Czech Republic. 3National Institute of Mental Health, Klecany, Czech Republic

dominika.radostova@fgu.cas.cz

Aims: The aim of this project is to develop a new one-trial associating task. We sought to produce a behavioral setup where animal readily learns to associate two distinct but close events in time - in one trial and without previous training.

Methods: We modified a light/dark shuttle-box environment so that rats almost completely preferred dark compartment. Following three days of habituation, each animal was presented with a loud sound that was followed, after 2-sec interval, by an electric foot-shock. An escape to the light compartment terminated foot-shock. Animals were re-tested after 24-hod when only sound was presented and animal reaction was recorded. We also recorded freezing behavior to assess contextual association with the apparatus.

Results: 30% of rats escaped into light compartment following the sound presentation on testing day - indicative of associative learning. Importantly, rats did not show the contextual fear measured by freezing behavior on testing day. Moreover, we found that details in setup and strain of rats affect successful preference of dark compartment during habituation.

Conclusions: our novel test is unique: 1) it lacks a need for learning a particular rule 2) our task addresses association of temporally segregated events and 3) it has a one-trial character.

This work was supported by GACR grant 17-04047S and AZV grant 17-30833A. Institutional support for IPHYS was provided by RVO: 67985823.

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LACK OF GEMC1/LYNKEAS FAVOURS NEURAL STEM CELL CHARACTERISTICS LEADING TO HYDROCEPHALUS

Konstantina Kaplani[1], Maria-Eleni Lalioti[1], Georgia Lokka[1], Christina Kyrousi[1], Marina Arbi[2], Evangelia Parlapani[1], Zoi Lygerou[2], Stavros Taraviras[1]

1Department of Physiology, Medical School, University of Patras, Greece;
2Department of General Biology, Medical School, University of Patras, Greece

kwnstantina.kaplani@gmail.com

Ependymal cells of the brain carry multiple motile cilia to ensure cerebrospinal fluid (CSF) propulsion throughout the brain. They constitute key components of the subventricular zone niche (SVZ) and surround the adult neural stem cells arranged in a pinwheel fashion. Ependymal cells are generated from neural progenitors, called radial glial cells (RGCs). Malformation of ependymal cells has been associated with CSF flow disturbances and hydrocephalus formation, in both mice and humans. Our findings reveal that GemC1/Lynkeas, member of the Geminin family, is the earliest known marker of RGCs, committed to the ependymal lineage.

Aim: Our aim is to further address the mechanisms regulating the fate decisions of RGCs and the identification of possible consequences of their dysregulation focusing on neurodegenerative diseases, like hydrocephalus. For this reason, we have generated GemC1/Lynkeas knockout mice (Methods).

Results: Our study demonstrates that GemC1/Lynkeas deficient mice exhibit complete lack of early committed and mature multiciliated ependymal cells in the SVZ, resulting in severe hydrocephalus. Moreover, cellular components of the niche are severely affected by the absence of GemC1/Lynkeas leading to impaired neurogenesis. Intriguingly, we have shown that GemC1-deficient cells exhibit altered cellular characteristics, thus uncovering their cell fate change towards a neural stem cell phenotype.

Conclusions: Our results show that GemC1/Lynkeas governs RGCs fate initiation to the ependymal lineage and the establishment of the SVZ niche. We provide a better molecular insight into ependymal cells formation and will serve as an ideal model for the mechanisms underlying the pathogenesis of hydrocephalus.

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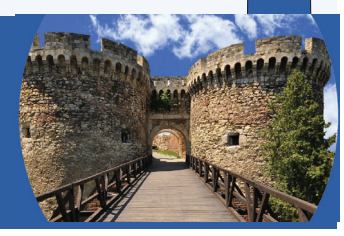

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CULTURAL BACKGROUND SHAPES BRAIN ACTIVITY AND ASSOCIATIONS ELICITED DURING LISTENING TO A NARRATIVE

Maria Hakonen[1,2], Arsi Ikäheimonen[1], Annika Hulten[3], Janne Kauttonen[1], Miika Koskinen[4], Fa-Hsuan Lin[5], Anastasia Lowe[1], Mikko Sams[1]; Iiro Jääskelainen[1]

1Brain and Mind Laboratory, Department of Neuroscience and Biomedical Engineering, Aalto University School of Science, Espoo, Finland, 2Advanced Magnetic Imaging Centre, School of Science, Aalto University, 3Imaging Language Laboratory, Department of Neuroscience and Biomedical Engineering, Aalto University School of Science, Espoo, Finland;
4Faculty of Medicine, University of Helsinki, Helsinki, Finland;
5Sunnybrook Research Institute, Department of Medical Biophysics, University of Toronto, Canada

maria.hakonen@aalto.fi

We studied whether cultural differences in the familial background shape how the brain processes a narrative, and how the narrative is interpreted.

We recruited 48 healthy volunteers who were fluent in Finnish. Half of the subjects had parents with a Finnish cultural background, whereas the other half had one or both parents with a Russian cultural background. The subjects listened to a 71-min narrative during ultra-fast fMRI. The narrative told a story of two protagonists, one with a Finnish and the other with a Russian background. Afterwards, the narrative was replayed in 101 segments, and the subjects were asked produce associations related to the previous segment. Between-subject similarities of brain hemodynamic activity were estimated using inter-subject correlation analysis. The similarity in how the narrative was interpreted was estimated by comparing the semantic relatedness of the associated words across the two groups in a semantic space (Word2Vec) generated from a large internet text corpora.

The cosine similarity of the associated words in the semantic space was different between the two groups. Further, there were between-group differences in inter-subject correlation of brain hemodynamic activity in the lateral occipital cortex, temporal cortices and precuneus.

Our results suggest that cultural differences in the familial background shapes how a person interprets a narrative and how their brains processed it. Differences in inter-subject correlation suggest that cultural familial background modulates processing of words and sentences, processing of the information accumulated across the narrative as well as mental imagery elicited by the narrative.

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BENEFICIAL EFFECTS OF *TRANS E*-VINIFERIN, A NATURAL POLYPHENOL, IN A MURINE ALZHEIMER DISEASE (AD) MODEL

Freyssin Aline [1], Serriere Sophie [2], Page Guylène [1], Tauber Clovis [2], Chassaing Damien [1], Vercouillie Johny [2], Perrin Flavy [3], Godet Julie [4], Bodard Sylvie [2], Guillard Jérôme [3], Fauconneau Bernard [1], Chalon Sylvie [2]*, Rioux Bilan Agnès [1]*

[1] University of Poitiers, EA3808 Neurovascular Unit and Cognitive Disorders, Poitiers, France, [2] ***University of Tours, INSERM U1253 Imagery and brain, Tours, France,*** *[3] University of Poitiers, UMR CNRS 7285 Institute of chemistry of Poitiers: Materials and Natural Resources, Poitiers, France, [4]* ***Poitiers University Hospital, Department of Pathology, Poitiers France***

aline.freyssin@univ-poitiers.fr

Aims: The purpose of this study was to compare curative effects of *trans* εviniferin and resveratrol in a murine model of AD. Indeed, we previously demonstrated that viniferin, a dehydrodimer of resveratrol, induced the disaggregation of $A\beta_{42}$ peptide and inhibited the inflammatory response in primary cellular model of AD. Moreover, it reduced size and density of amyloid deposits and decreased reactivity of astrocytes and microglia, after a weekly intraperitoneal injection at 10 mg/kg from 3 to 6 months of age of APPswe/PS1dE9 mice. These promising results demonstrating preventive role of viniferin had to be completed by evaluation of curative effects.

Methods: In this study, we compared effects of viniferin and resveratrol in APPswe/PS1dE9 mice, after a weekly intraperitoneal injection at 20 mg/kg from 7 to 11 months. Before the first injection and after the last one, cognitive status was evaluated using water-maze. At 11 months, the levels of neuroinflammation and amyloid load in the mice brain were evaluated by positron emission tomography, using [(18)F]DPA-714 to measure neuroinflammation and [(18)F]AV-1 for amyloid load. Amyloid deposits and neuroinflammation were also visualized *ex-vivo* after euthanasia, by immunolabelling of amyloid peptide, astrocytes and microglia.

Results: We demonstrated that viniferin had higher curative effects than resveratrol to reduce amyloid deposits and neuroinflammation in these Alzheimer mice. However, it seemed slightly less efficient on cognitive decline between 7 and 11 months than resveratrol.

Conclusion: Viniferin seems to have both preventive and curative effects in AD and could be a relevant therapeutic candidate for this disease.

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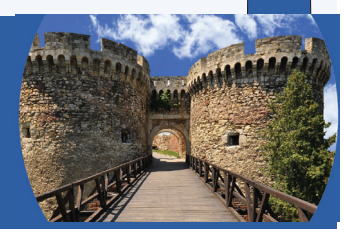

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PHYSICAL EXERCISE PREVENTS OBESOGENIC DIET-INDUCED EMOTIONAL AND SPATIAL DEFICITS.

Lafenetre, P., Alfos, S., Dinca, A., Ferreira, G.

Univ. Bordeaux, INRA, Bordeaux INP, NutriNeuro, UMR 1286, F-33000, Bordeaux, France

pauline.lafenetre@enscbp.fr

The increase of the obesity pandemic is favored by an overconsumption of energy-dense food and a sedentary lifestyle. While obesity is associated with adverse anxiety and cognitive consequences, physical exercise improves physiological and behavioral outcomes. The aim of this study was to assess the potential beneficial effects of physical exercise on emotional and cognitive deficits induced by obesogenic high-fat diet (HFD) consumption in mice.

At weaning, mice were individually housed and divided into four groups according to their diet (HFD or control diet) and housing conditions (sedentary or running). Eight weeks later, mice were submitted to the elevated plus maze to evaluate anxiety-like behavior and then to the Morris water maze to assess spatial memory and flexibility. Moreover, the expression of plasticity markers (IGF1, IGFR and BDNF) was quantified in the hippocampus.

Physical exercise was able to prevent weight gain and fat storage induced by HFD. In addition, physical exercise alleviated HFD-induced increased anxiety levels and restored impaired spatial memory by favoring the use of spatial strategies. However, impairment of spatial flexibility was not rescued by physical exercise in HFD-fed mice. Interestingly, HFD intake decreased hippocampal mRNA levels of IGF1, IGFR and BDNF that were normalized by exercise.

Our approach points out that HFD exposure can induce behavioral alterations that can mainly be prevented by physical exercise, likely through improvement of hippocampal plasticity.

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THE NMDA ANTAGONIST MEMANTINE ATTENUATES THE OKADAIC ACID (ICV) INDUCED NEUROTOXICITY IN RATS

Mariam Chighladze[1], Gela Beselia[2], Khatuna Rusadze[2]

1 I.Baritashvili Center of Experimental Biomedicine, Tbilisi, Georgia. 2 Akaki Tsereteli State University, Kutaisi, Georgia

makachighladze@yahoo.com

Alzheimer's disease (AD) is a neurodegenerative disease that causes progressive cognitive and behavior deterioration over age 65. It is supposed that breaking the balance between tau protein phosphorylation and dephosphorylation will lead to AD-like tauopathy. Okadaic acid (OA) is a potent and selective inhibitor of PP1 and PP2A. It was suggested that intracerebral injection of OA would provide a useful model of AD.

In the present study, intracerebroventricular (ICV) injection of okadaic acid (OA) in rats was used as a memory impairment and hippocampal neurodegeneration animal model. The possible beneficial effect of memantine - NMDA (N-methyl-D-aspartate) receptor antagonist on the OA-induced spatial memory impairment was examined in Morris water maze (MWM).

The neuroprotective potential of memantine on OA-induced structural and molecular changes in the hippocampus and medial septum (MS) was evaluated by immuno and Nissl staining.

Nissl staining of hippocampal sections showed that the number of pyramidal cells in the CA1 and CA3 regions of the hippocampus in the control group is significantly higher than that in the OA injected rats. The immunohistochemical study showed that the number of AChE sensitive neurons in different regions of the hippocampus and decreased the number of ChAT and PV-sensitive GABAergic neurons in medial septal nucleus and chronic administration of memantine effectively attenuated OA induced neuropathological changes in the hippocampus and MS.

The behavioral results showed that bilateral injection of OA causes a deficiency of spatial memory and that the chronic exposure of memantine can prevent a deficiency of spatial memory.

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PRESTIMULUS ALPHA POWER PREDICTS PERCEPTUAL SUPPRESSION

E. Poland[1], A. Bhonsle[1], I. Steinmann[1] & M. Wilke[1,2,3]

[1] Department of Cognitive Neurology, UMG, University Medicine Goettingen, , Goettingen, Germany. [2] DFG Center for Nanoscale Microscopy & Molecular Physiology of the Brain (CNMPB), Göttingen, Germany. [3] German Primate Center, DPZ, Leibniz Institute for Primate Research, Goettingen, Germany

eva.poland@med.uni-goettingen.de

Aims: The amplitude of prestimulus alpha oscillations over parieto-occipital cortex has previously been shown to predict visual detection performance of masked and threshold-level stimuli, and lower alpha amplitudes have been associated with higher cortical excitability. Here, we examined whether prestimulus alpha oscillations reflect visual awareness during perceptual suppression.

Methods: We analysed prestimulus EEG alpha oscillations of healthy participants (N=27) recorded in the context of a Generalized Flash Suppression (GFS) paradigm, a visual illusion during which salient target stimuli are rendered subjectively invisible on a portion of trials while physical stimulation is kept constant.

Results: Unlike for masking or threshold paradigms, alpha power (8-12Hz) prior to surround stimulus onset was significantly higher for trials in which the targets remained subjectively visible compared to trials during which the targets were perceptually suppressed. Phase synchrony in the alpha band was also lower for perceptual suppression trials within parieto-occipital cortex as well as between parieto-occipital and frontal cortex. The individual level of prestimulus alpha power strongly correlated with the individual degree of trial-to-trial variability quenching following stimulus onset.

Conclusions: Our results indicate that visual awareness correlates of perceptual suppression paradigms such as GFS differ substantially from those of masking or threshold paradigms.

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PERIODICITY PITCH RECOGNITION IN COMPLEX HARMONIES ON EEG TIMELINE DATA

Maria Heinze[1,2], Lars Hausfeld[2], Rainer Goebel[2], Frieder Stolzenburg[1]

1Harz University of Applied Sciences, Wernigerode, Germany. 2Maastricht University, Maastricht, Netherlands

mheinze@hs-harz.de

During the hearing process in ear and brain, an acoustic stimulus, e.g. a musical harmony, is transformed in a highly non-linear way. We study this by comparing the frequency spectrum of an input stimulus and its response spectrum in the auditory processing stream using the frequency following response (FFR).

Aims. The goal is to develop a model how the human brain perceives and processes musical sounds. Using EEG, we investigate whether periodicity pitches of complex harmonies (related to their missing fundamentals) are added in the auditory brain stem by analyzing the FFR (Lee et. al. 2015). We use three-tone stimuli (common triads) because of their musical significance.

Methods. While watching a muted documentary, 17 healthy adult participants hear triads and single tones. Note that the sought-for periodicity pitch frequencies do not physically exist in the frequency spectra of the stimuli.

Results. The frequency spectra of the EEG response show, that the periodicity pitch frequency calculated beforehand according to Stolzenburg (2015) as well as its double occurs with an accuracy of +/-3Hz. In the frequency spectrum of the G major chord, the most dominant frequencies belong to the fourth and third partial. The spectral characteristics of the response to that G major chord show the desired peaks at the frequencies ~49Hz and ~98Hz.

Conclusions. Although the auditory brain stem shows low-pass characteristics (Skoe et. al. 2010), our experiments suggest that higher frequencies and complex harmonic sounds (triads) result in the appearance of the periodicity pitch in the auditory brain stem response.

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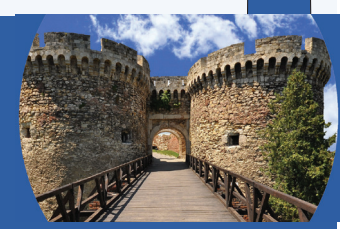

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A GLUTAMATERGIC NETWORK LINKS BASAL FOREBRAIN AND MIDBRAIN CIRCUITS DURING LOCOMOTION

Petra Mocellin[1], Pavol Bauer[1], Dennis Dalügge[1], Falko Fuhrmann [1], Hiroshi Kaneko[1], Christina Müller[1], Stefan Remy[1,2]

[1]German Center for Neurodegenerative Diseases, Neuronal Networks, Bonn, Germany. [2]University of Bonn Medical Center, Department of Epileptology, Bonn, Germany

petra.mocellin@dzne.de

Locomotion is a fundamental behavior that comprises different specialized neuronal networks. Nevertheless, how locomotion is initiated and which networks are involved in the control of its onset and speed is not fully understood. Glutamatergic neurons in the medial septum and diagonal band of Broca (MSDB) are known to evoke locomotion when stimulated. During locomotion they provide speed-correlated inputs to the hippocampus and the entorhinal cortex. However, how MSDB connects to other brain areas involved in locomotor execution in not known. We hypothesize that glutamatergic projections from MSDB provide locomotion-related input to striatum that is further relayed to motor cortex via the ventral tegmental area (VTA). In this project we aim at dissecting the MSDB-VTA-striatal circuit and to find out whether the MSDB VGluT2+ inputs to VTA are involved in the execution of locomotion.

Synaptic targets of VGluT2+ axons where identified in acute VTA slices from VGluT2 Cre mice using optogenetic activation with subsequent tetrodotoxin/4-AP and glutamate blocker application. In vivo optogenetics, fiberphotometry and pharmacology were applied to dissect the circuitry.

The experiments performed in brain slices confirmed the existence of a monosynaptic glutamatergic connection between MSDB and VTA. Fiberphotometry data showed that VTA neurons receive MSDB glutamatergic inputs that occur concurrently with movement onset. Optogenetic activation of VGluT2+ VTA neurons reliably initiated locomotion.

Our data provide evidence that a glutamatergic network is linking basal forebrain and midbrain circuits during locomotion.

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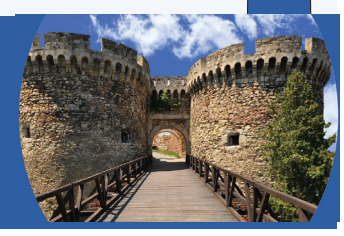

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A SYSTEMS APPROACH TO IDENTIFY CIRCULATING MICRORNAS AS MARKER FOR COGNITIVE FLEXIBILITY

M.R. Islam[1], L. Kaurani[2], T. Berulava[1], U. Heilbronner[3], M. Budde[3], T. Schulze[3], P. Falkai[4], F. Sananbenesi[5] and A. Fischer[1,2]

1 German Center for Neurodegenerative Diseases, Department for Epigenetics and Systems Medicine in Neurodegenerative Diseases, Göttingen, Germany;
2 University Medical Center Göttingen, Dept. For Psychiatry and Psychotherapy, Göttingen, Germany;
3 Institute of Psychiatric Phenomics and Genomics, Medical Center of the University of München, München, Germany;
4 Department of Psychiatry and Psychotherapy, Medical Center of the University of München, München, Germany;
5 Research Group for Genome Dynamics in Brain Diseases, Göttingen, Germany

rezaul.islam@dzne.de

Aging is the major risk factor for cognitive decline and dementia. However, there is a substantial inter-individual variability amongst individuals and while some develop age-associated memory impairment others undergo "healthy aging" accompanied by preserved cognitive function. Easily accessible blood markers that would reflect early molecular changes in the brain at pre-clinical stage of dementia and reliably predict cognitive decline are therefore of great importance.

In this study, we employ a longitudinal approach to test the hypothesis that circulating microRNA levels can inform about the cognitive status. We investigated two cohorts of mice from 12 to 16.5 month of age in a longitudinal manner. One group was housed in home cages, while the other was subjected to spatial reference memory testing every 1.5 months. Target region during the spatial reference memory training was changed at each time point, thereby, forcing mice to employ their cognitive flexibility to learn new task at every 1.5 months. Along with behavioral data, blood was collected at 4 time points (12, 13.5, 15 and 16.5 months) and small RNA sequencing was performed.

We identified smallRNA signature linked to cognitive function and could demonstrate via mechanistic studies that these microRNAs regulate cognition. Moreover, via cross-correlation to published datasets and analysis of a deeply phenotyped cross-sectional human cohort we were able to demonstrate that the detected microRNAs also predict cognitive function in humans.

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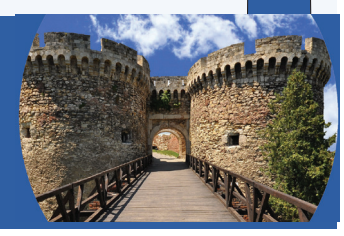

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CORRELATING THE ACTIVITY OF HIPPOCAMPAL NEURONAL ASSEMBLIES WITH BEHAVIOR IN FREELY MOVING MICE

Pavol Bauer, Falko Fuhrmann, Stefan Remy

German Center for Neurodegenerative Diseases, Germany

pavol.bauer@dzne.de

Aims: Understanding the neuronal basis of behavior is a major challenge for current neuroscience. To understand how activity of neuronal assemblies relates to behavioral patterns we firstly need to quantify behavior at the most unconstrained setting. During recordings in head fixed animals the variety of behavioral freedom is clearly constrained and the animal can only exhibit a limited amount of actions. Controlled experiments in freely moving animals therefore enable to record a broader range of behavior under the influence of environmental stimuli. Second, we need to understand how cellular activity patterns are engaged during freely moving behavior using imaging techniques that are able to cope with the necessary degree of flexibility.

Methods: We record the hippocampal population Ca2+ activity in a chronic mouse preparation using a fast high-resolution miniaturized two-photon.

Results: During the experiment the animal is allowed to move freely in a circular arena, while a 3d-depth camera captures the animal's pose dynamics. We then analyze the behavioral data using a novel machine learning techniques and extract precise behavioral information from the depth camera information. We then correlate the behavioral and functional data and seek to determine whether a specific relationship with the neuronal activity in the hippocampal formation patterns exists.

Conclusion: The approach presented here is highly applicable to a variety of experimental studies and allows for discovery of causal links between activity patterns and a variety of behavioral parameters

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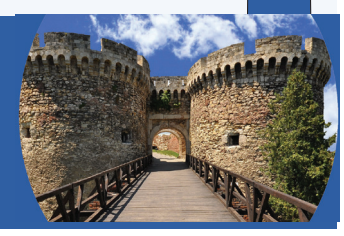

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WORKING MEMORY TRAINING ON COGNITIVE FLEXIBILITY IN BOTH WOMEN AND FEMALE MICE: TRAINING GAINS, TRANSFER AND THE NEUROBIOLOGICAL BACKGROUND

Vasiliki Stavroulaki[1], Maria Zafeiri[2], Panagiotis Bitsios[1], Stella G. Giakoumaki[3] and Kyriaki Sidiropoulou[4]

[1]Medical school, University of Crete, Heraklion /Crete, Greece. [2]Department of Biological Applications & Technology, University of Ioannina, Ioannina, Greece. [3]Department of Psychology, University of Crete, Rethymno /Crete, Greece. [4]Department of Biology, University of Crete, Heraklion /Crete, Greece

vickystavroulaki@gmail.com

Current research aims to determine whether working memory training can enhance cognitive flexibility in both human and mice.

The human study included thirty-eight healthy women, who were divided in: a) a control (no cognitive training), b) a partially adapted (partial administration of an executive working memory task, the Letter Number Sequencing, for six consecutive days) and c) a fully adapted group (administration of the entire test for the same period). Following training, all participants were tested in another cognitive flexibility task; the Intra-Extra Dimensional Set Shift (ID/EDS).

Results showed that the fully adapted group had lower response latency and made fewer attempts to complete the stages of the ID/EDS test, compared with the other two groups. There were also significant correlations between the tests used. In the animal study, a similar experimental design was applied (utilizing the delayed alternation task for WMT). Fourteen female mice are divided into a naïve (remained in their home cage), a non-adaptive (learned to alternate arms, but without any delays) and an adaptive group (performed the alternation procedure with increasing delays). Following WMT, all mice underwent the Attentional Set - Shifting Task.

Results showed that the adaptive group had better performance at the extradimensiontal shift stage, compared to the non-adaptive group. The effect of WMT on dendritic spine morphology of prefrontal cortex and hippocampal neurons was also studied. In conclusion, our results indicate the value of WMT, as a tool for general cognitive enhancement in a cross species study.

This research work was supported by the Special Accounts for Research Grant to SGG and KS (GA.no.10214), by the Hellenic Foundation for Research and Innovation (HFRI) and the General Secretariat for Research and Technology (GSRT), under the HFRI Phd Fellowship grant (GA.no.4780).

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BEHAVIORAL AND NEUROCHEMICAL EFFECTS OF OLIVE OIL TOTAL PHENOLIC CONTENT AND SIDERITIS EXTRACT IN FEMALE MICE.

Poulogiannopoulou E.[1], Sotiropoulos M. G.[1], Paravatou R. [1], Dimitriadou M.[1], Perrea D. [2], Tsarbopoulos A. [1,3], Skaltsounis AL.[4], N. Kokras [1,5], C. Dalla[1]

[1]Department of Pharmacology, Medical School, National and Kapodistrian University of Athens, Athens, Greece. [2]Laboratory for Experimental Surgery and Surgical Research "N. S. Christeas", Medical School, National and Kapodistrian University of Athens, Athens, Greece. [3]Bioanalytical Department, GAIA Research Center, The Goulandris Natural History Museum, Kifissia, Greece. [4]Department of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece. [5]First Department of Psychiatry, Eginition Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

eleni.poulo@gmail.com

The neuropsychopharmacology of the Mediterranean diet's individual components, such as olive and herbal tea extracts, remains largely unexplored. The aim of this study was to determine the cognitive and behavioral effects of olive oil total phenolic content (TPC) and sideritis (SID) extracts in female mice, and to identify the associated neurochemical changes in the hippocampus and the prefrontal cortex.

Both extracts were administered intraperitoneally in two doses (TPC: 10 and 30mg/kg, SID 50 and 150mg/kg) in adult C57BL/6 female mice. Mice received TPC, Sideritis or vehicle treatment for 7 days and were subjected to the Open Field, the Novel Object Recognition (NOR) and the Tail Suspension Test (TST). Prefrontal cortex and hippocampus were dissected and used for analysis of neurotransmitters and aminoacids with HPLC-ED.

TPC in both doses enhanced vertical activity and center entries in the open field test, which could indicate an anxiolytic-like effect of the extract. In addition, TPC enhanced non-spatial working memory and in high doses it exerted antidepressant effects. On the other hand SID in high doses decreased remarkably overall activity. Locomotor and exploratory activities were closely associated with cortical increase of 5-HT turnover induced by both treatments. Cognitive performance was linked to glutamate level changes. Furthermore, TPC reduced cortical taurine levels, while Sideritis reduced cortical aspartate levels.

In conclusion, TPC seems to improve cognition and reduce anxiety, whereas SID has sedative effects in high doses. Both compounds act in the brain, but their specific actions and properties merit further exploration.

Acknowledgments: TreatAD

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CHEMOGENETIC EVIDENCE OF A NOVEL NEURONAL PATHWAY CONVEYING SOCIAL INPUT FROM A CONSPECIFIC TO HIGHER BRAIN CENTERS IN RAT

Dávid Keller[1], Emese A. Fazekas[2], Arpád Dobolyi[1,2]

1Laboratory of Neuromorphology, Department of Anatomy, Histology and Embryology, Semmelweis University, Budapest, 2MTA-ELTE Laboratory of Molecular and Systems Neurobiology, Department of Physiology and Neurobiology, Eötvös Loránd University and the Hungarian Academy of Sciences, Budapest

keller.david8@gmail.com

Aims: In a previous study, we determined the posterior intralaminar complex of the thalamus (PIL) as a relay station of socially relevant sensory information innervating and activating oxytocin-secreting neurons upon social encounter. Our present aim was to identify and functionally characterize neuronal projections from the PIL during stress-free social interaction in rats.

Methods: We examined the interactions between familiar female rats. The brain activation patterns were determined following direct interaction, and also with the exclusion of physical interaction using the c-Fos technique. We also determined the effect of chemogenetic stimulation of the PIL using the DREADD technique on the social behavior and the brain activation pattern. In addition, anterograde tract-tracing from the PIL was performed.

Results: We found that neurons in the PIL project to different elements of the social brain network, such as the somatosensory and the infralimbic cortices, the medial amygdala, the preoptic area, the paraventricular and dorsomedial hypothalamic nuclei. Significantly higher level of activation upon social encounter was found in the medial amygdala, the somatosensory and infralimbic cortices. The chemogenetic stimulation of the PIL resulted in the activation of the infralimbic and somatosensory cortices. Stimulation of the PIL also influenced the behaviour of the animals as it increased the duration of social interactions.

Conclusion: The results suggest that the PIL may convey socially relevant information to several other brain regions and contribute to the regulation of the complex neuronal mechanism of social behaviors.

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CHARACTERIZATION OF ENDOCANNABINOID SYSTEM IN A NEW MODEL OF FRONTOTEMPORAL DEMENTIA (FTD)

Santos-García I[1-3],Rodríguez-Cueto [1-3],García-Toscano L[1-3],Fernández-Ruiz J[1-3], De Lago E[1-3]

1Instituto Universitario de Investigación en Neuroquímica, Departamento de Bioquímica y Biología Molecular, Facultad de Medicina, UCM, Madrid, España;
2Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, España;
3 Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, España.

isantosg@ucm.es

Frontotemporal dementia (FTD) is a heterogeneous group of progressive neurodegenerative disorders of early onset, characterized by neuronal degeneration in the frontal and temporal lobes, which causes deterioration in cognition, personality, social behavior and language. Around 65% of the cases are characterized for the presence of TDP-43 aggregates, a protein that has been also associated with the development of amyotrophic lateral sclerosis (ALS). Nowadays both pathologies are considered a continuous clinical spectrum with common pathogenic mechanisms and without an effective treatment. In the case of ALS there are evidences that the endocannabinoid system (ECS) and its modulation could delay the progression of the disease. In this context, the aim of the present study was to improve the characterization of the phenotype of a new FTD mice model, which overexpress TDP-43 protein exclusively in the forebrain under the control of CaMKIIα. promoter (Kuen-Jer T., et.al., J.Exp.Med.,2010) in which had been previously explored some cognitive deficits at P60 and P90. However, our study was focused to improve the knowledge of possible cognitive impairments until P365 including emotional and behavioural aspects that have not been evaluated previously. Moreover, we are interesting in checking the status of the ECS at these stages in several brain areas directly related to the behavioural alterations. First, we confirmed that FTD mice exhibited behavioral signs of this disease, such as: (i) disinhibited social behaviour measured in the social interaction test; (ii) cognitive impairment detected in T-maze, Water-Morris maze and novel object recognition tests; and (iii) elevated stereotyped responses, as well as impulsivity recorded in the elevated plus maze test. At histological level we observed an increase of neuroinflammation markers such as GFAP or Iba-1 in areas related with the behavioral sings like prefrontal cortex or CA1 layer and dentate gyrus of hippocampus, and also the presence of TDP-43 aggregates on these areas. The analysis of the ECS in the forebrain revealed a decrease in mRNA levels of the degradation enzyme FAAH in the prefrontal cortex and striatum, and an increase in the synthesis enzyme NAPE-PLD in the hippocampus, responses in both cases compatible with elevated levels of endocannabinoids in these structures, which may be interpreted as an endogenous protective responses. In summary, our data reveal that FTD mice present behavioural disturbances similar to suffered by patients with this pathology and a dysregulation of some key elements of the ECS in areas related with these behavioural and cognitive alterations. These results suggest the interest of modulation of the endocannabinoid tone by inhibiting endocannabinoid inactivating enzymes or even by using non-selective agonists (e.g. Δ9-THC) capable to activate both CB1 and CB2 receptors, for the treatment of FTD.

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THE PSYCHOMOTOR VIGILANCE TASK (PVT) PROVIDES A HIGHLY TRANSLATIONAL BEHAVIORAL PARADIGM FOR TESTING COGNITIVE IMPAIRMENT AND CHOLINERGIC PHARMACOLOGICAL INTERVENTIONS IN YOUNG AND AGED RATS

Bali, Zsolt Kristóf[1,3], Bruszt, Nóra[1], Nagy, Lili Veronika[1,2], Bodó, Kornélia[4], Engelmann, Péter[4], Göntér, Kitti[1], Tadepalli, Sai Ambika[1], Hernádi, István[1,2,3]

1Translational Neuroscience Research Group, Centre for Neuroscience, Szentágothai Research Center, 2Department of Experimental Neurobiology, Faculty of Sciences, 3Grastyán Endre Translational Research Center, and 4Institute of Immunology and Biotechnology, Medical School, University of Pécs, Hungary

bali.zsolt.k@gmail.com

The psychomotor vigilance task (PVT) is a simple and widely used behavioral paradigm for the assessment of sustained-attention in humans. Furthermore, it is suggested that PVT also detects cognitive deficits in neurocognitive disorders. We adapted the PVT for rats to test its translational potential and validity in evaluating the efficacy of cognitive enhancers.

Aged (>30 m.o.) and young adult (12-16 m.o.) rats were trained for PVT in operant conditioning boxes. The animals had to wait for the onset of a visual stimulus with a random delay (0-5s), then had to respond with a fast lever-press. In young rats, we tested the amnestic effects of scopolamine (0.1 mg/kg), and its reversal by alpha7 nicotinic agonist PHA-543613. Aged rats were treated with PHA-543613 (0.3-3.0 mg/kg) with no prior amnestic treatment. Neurological status of aged rats was verified with post-mortem qPCR indicating altered cytokine and BDNF levels in their brain.

In comparison with young rats, aged animals showed significantly slower reaction times (RT), and performed less trials correctly, especially when stimuli appeared with long delays. Alpha7 nicotinic agonist PHA-543613 dose-dependently improved RT of aged rats, especially when stimuli appeared with very short delay (unexpected stimuli). Young rats after scopolamine treatment performed more premature trials and less correct trials. Scopolamine also increased RT of young rats, which effect was reversed by PHA-543613.

Results showed that PHA-543613 improved the reaction time in both models of cognitive impairment. Thus, we demonstrated that PVT is eligible for translational pharmacological investigations in rodents.

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HISTAMINE IMPROVES MICE ROTA-ROD PERFORMANCE THROUGH H1 AND H2 RECEPTORS IN THE CEREBELLAR VERMIS

B. Silva-Marquesa, E.M. Guilhermea, A.C.L. Gianlorençoa R. Mattiolia

Laboratory of Neuroscience, Physiotherapy Department, Center of Biological Sciences and Health, Federal University of Sao Carlos, Sao Carlos, Brazil

silvamarquesufscar@gmail.com mattioli@ufscar.br

Aims: We've conducted an experiment to investigate the dose-dependent effects of histamine, H1-receptor antagonist chlorpheniramine and H2-receptor antagonist ranitidine microinjected in the cerebellar vermis on motor performance and motor learning in mice.

Methods: We used Swiss albino mice maintained in a thermoregulated environment. The drugs used were histamine (0.54nmol, 1.36nmol, 2.72nmol and 4.07nmol), chlorpheniramine or CPA (0.016 nmol, 0.052 nmol, 0.16 nmol), ranitidine (0.57 nmol, 2.85 nmol e 5.7 nmol) and saline 0.9%. After being anesthetized, a guide cannula was implanted into the cerebellar vermis following coordinates from the mouse brain atlas of Paxinos and Franklin. The protocol was divided in five steps, which were named habituation, microinjection, stage 1, stage 2, and stage 3, where they were placed in rota-rod for 3 times, with 5 minutes of rest between each time. The protocol was repeated 4h later for stage 2 and repeated again 24h later for stage 3. Statistical analysis included the homogeneity test and multi-factor analysis of variance followed by Duncan's Multiple Range test. A p value of ≤0.05 was required for significance.

Results: The results showed a possible facilitation of histamine at the highest dose in the evaluation of learning and motor performance in the rota-rod. In addition, the results showed an impairment when tested at the 0.052 dose of CPA and at the lowest doses of ranitidine.

Conclusions: This suggests that cerebellar histaminergic projections are involved in motor learning and make a modulating role in the cerebellar circuit to ensure that movements are performed efficiently.

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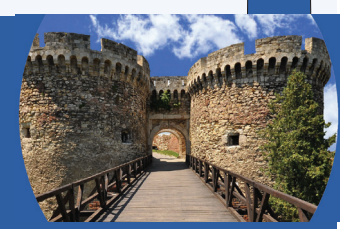

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ORGANIZATIONAL ROLE OF ESTRADIOL AND ESTROGEN RECEPTORS ON SEXUAL AND FEEDING BEHAVIORS

Marraudino M.[1], Paiano M.[1], Bonaldo B.[1], Farinetti A.[1], Ponti G.[1], Panzica GC.[1], Collado P. [2], Gotti S[1].

1Neuroscience Institute Cavalieri Ottolenghi NICO, Dept of Neuroscience´ Rita Levi Montalcini´ , University of Turin, Turin, Italy. 2Universidad Nacionald de Educacion a Distancia UNED, Dept of Psychobiology, Madrid, Spain

marilena.marraudino@unito.it.

Many hypothalamic systems, that control metabolism and reproduction, are programmed and stabilized during critical periods of development by many factors, including gonadal steroid. In particular, estradiol (E2) appears to have an important role on organization of these circuits. E2 during the early stages of life is able to regulate the expression of sexually dimorphic behaviors, such as sexual and feeding behaviors. E2 acts through three different receptors: ERα, ERβ and GPR30.

To understand the role of ERs, we treated male and female CD1 mice from postnatal day (PND) 5 to PND12 with subcutaneous injections of vehicle (corn oil), E2 and it associated with selective antagonists of ERs (MPP; PHTPP; G15) alone or together (mix). We analyzed, during the development, different physiological parameters related to food intake and reproductive system. When adult, we tested these animals with Y-maze and sexual behavior.

Females treated with E2 present a significant sexual preference for other females, an altered estrus cycle, and an increased daily feed efficiency. The treatments with G15 alone or in combination (mix) altered all the considered parameters in male and female mice. On the contrary MPP and PHTPP showed sexually dimorphic effects. MPP modified, in males, feeding parameters, but not to reproduction, whereas PHTPP modified parameters related to reproduction, but not to feeding. In females the situation was exactly the reverse.

In conclusion, our data demonstrate that E2 has a strong organizational role on different neuroendocrine systems, acting primarily on GPR30 and in a sexually different way on ERα and ERβ.

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MULTISTORY ENRICHED ENVIRONMENT COULD INCREASE PHYSICAL ACTIVITY AND IMPROVE BRAIN FUNCTION

Shinya Yanagita, Natsuko Kubota
Tokyo University of Science, Tokyo, Japan
yanashin@rs.noda.tus.ac.jp

Numerous studies have shown that enriched environments (EE) could be effective for experimental rodents to improve some brain functions related to stress response and anxiolytic effect, and speculating that playfulness in EE might influence these beneficial effects. On the other hands, it is well known that increasing levels of physical activity could have the beneficial effects as well as EE. Taken together with these evidence, the question arises: Which is effective for improvement of brain function between playing or physical activity? The aims of present study is to answer the question using multistory enriched environment (Multi-EE), which can increase physical activity in rats.

We originally made Multi-EE, which are consisted by three stories. The male Wistar rats housed the Multi-EE or normal EE for 4weeks in group housing conditions (3 rats per cage). The rats housed in Multi-EE allow to access to the three stories freely by ladders. Daily physical activity were recorded using implantable accelerometer. Following 4weeks, brain monoamine levels, which is involved with stress response and anxiolytic effect, were measured by HPLC in several brain regions.

The Multi-EE significantly increased physical activity compared to normal EE. Furthermore, the Multi-EE housing were able to change the brain monoamine levels, such as serotonin and dopamine. The changing levels of these monoamine are known to have some beneficial effects for stress response and anxiety. Therefore, the results of present study suggest that increasing levels of physical activity by Multi-EE could influence some brain functions.

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EFFECT OF SHORT DURATION OF SLEEP DEPRIVATION ON BRAIN MONOAMINERGIC NEUROTRANSMITTERS, PHYSICAL INDICES, AND BEHAVIOR IN RATS

Daisuke Matsunaga[1], Miho Sato[1], Fumiharu Togo[2], Takayuki Ishiwata[1]

1Graduate School of Community Human & Services, Rikkyo University, Saitama, Japan . 2Graduate School of Education, University of Tokyo, Tokyo, Japan

19wd005h@rikkyo.ac.jp

We investigated the influences of the effects of irregular work style on brain monoaminergic neurotransmitters and behavior in rats.

Male Wistar rats were housed individually. Telemetry devices, which record core body temperature (Tc), heart rate, and locomotor activity (Act), were embedded into the rats, intraperitoneally. The rats were divided into three groups: day shift (DS), night shift (NS), and control (C). All groups were exposed to sleep deprivation cage with scraper (SDR-C, Melquest, Japan). The DS group worked only during the dark phase. The NS group worked from the dark phase through the light phase. The C group did not work on the scraper. After 1 week, the rats underwent open field tests (OFT). After 2 weeks, they were sacrificed for analyzing monoaminergic neurotransmitters.

Act in the NS group was higher than that in the DS group, but range of Tc between the light and dark phase was lower in the NS group than in the DS group. NS showed disturbances in Tc even during the rest period, which is known as internal desynchronization. Moreover, the NS group had decreased levels of noradrenaline in the suprachiasmatic nucleus and dopamine in the substantia nigra. The time in the center and line crossing of the open field was decreased in the C group. However, no differences were noted for these parameters between the DS and NS groups.

Our study shows that there is a possibility that sleep deprivation can negatively impact brain monoaminergic neurotransmitters.

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EFFECT OF HEAT ACCLIMATION ON BRAIN MONOAMINES AND EMOTIONAL BEHAVIOR IN RATS

Hikaru Nakagawa[1,2] , Daisuke Matsunaga[1], Takayuki Ishiwata[1]

1Graduate School of Community Human & Services, Rikkyo University, Saitama, Japan. 2Japan Society for the Promotion of Science, Tokyo, Japan

17wd003l@rikkyo.ac.jp

We aimed to investigate heat acclimation-induced changes in emotional behavior and neurochemistry of monoamines in the rat brain.

Rats were exposed to heat for 3 h (3H), 1 day (1D), 7 days (7D), 14 days (14D), 21 days (21D), or 28 days (28D). The dorsomedial hypothalamus (DMH) and frontal cortex (FC) of all rats were homogenized, and the levels of brain monoamines were measured. Additionally, rats exposed to heat for 3H, 14D, or 28D underwent the open field test (OFT) to assess emotional behavior.

Noradrenaline level was increased in the DMH at 21D. Dopamine level was increased in the DMH and FC at 28D. Serotonin level was decreased in the DMH at 1D, 7D, and 14D and in the FC without 28D. Body weight was decreased at 14D and 28D. In OFT in a heated environment, time spent grooming (TG) only changed in the 3H and 14D groups, whereas in a temperate environment, TG increased in all the experimental groups. More time was spent in the center square by rats treated for 3H and 28D in a temperate condition. The number of rearing increased in the 28D group in the temperate environment. The number of line crossing did not change in either environment.

These results suggest that heat acclimation affects brain monoamines and changes emotional behavior. These changes might be beneficial for rats to live in hot environments.

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ENHANCEMENT OF HIPPOCAMPAL NEUROGENESIS INDUCED BY ENVIRONMENTAL ENRICHMENT DOES NOT DEPEND ON INCREASED PHYSICAL ACTIVITY IN MICE

Daisuke Funabashi[1], Ichiro Kita[1], Takeshi Nishijima[1]
[1]Hum Health Sci, Tokyo Met Univ, Tokyo, Japan

fnbs6186@yahoo.co.jp

Aims: Exposure to environmental enrichment (EE) has positive effects on brain function, including hippocampal neurogenesis, in rodents, even though a running wheel equipment is not included. Here we hypothesized that EE increases home-cage activity in rodents, which subsequently contributes to improving brain function. However, it is unknown whether EE increases home-cage activity in rodents. The purpose of this study was to investigate effects of EE in the absence of running wheel on home-cage activity in mice.

Methods: Male C57BL/6J mice (10 weeks old) were randomly assigned to either a control (C) or an enrichment (E) group. C mice were housed in a standard cage throughout the experiment, while E mice were housed in a standard cage for a week and EE cage (large cage with toys) for two weeks in this order. Home-cage activity was recorded by an implantable accelerometer, nanotag, which enables us to record physical activity in rodents in any situation. After the end of intervention, mice were anesthetized and the brain were removed for immunohistochemical examination of hippocampal neurogenesis.

Results: EE without running wheel increased doublecortin-positive immature neuron, replicating EE-induced hippocampal neurogenesis. However, contrary to our hypothesis, EE did not increase home-cage activity in mice.

Conclusions: These results suggest that enhancement of hippocampal neurogenesis induced by EE does not require increased physical activity in mice.

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EXERCISE HABIT ENHANCES THE EXPRESSION OF BRAIN-DERIVED NEUROTROPHIC FACTOR IN THE HIPPOCAMPUS ACCOMPANIED BY EPIGENETIC CHANGES IN SENESCENCE-ACCELERATED MICE PRONE 8

Hiroshi Maejima[1], Xiang Li[2], Takahiro Inoue[2], and Masataka Hayashi[2]

1Graduate School of Health Sciences, Hokkaido University, Sapporo, Japan. 2Department of Rehabilitation Science, Faculty of Health Sciences, Hokkaido University, Sapporo, Japan

maeji@hs.hokudai.ac.jp

Aims: It is well recognized exercise increases the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus and beneficially contributes to cognitive function accompanied by epigenetic changes. Specifically, the activity balance between histone acetyltransferases (HATs) and histone deacetylases (HDACs) regulate histone acetylation and modulate gene transcription. The objective of the present study was to assess the effect of long-term exercise on the expression of BDNF, tropomyosin receptor kinase B (TrkB) and p75, and the activity of HATs and HADCs in the degenerative hippocampus.

Methods: We used the senescence-accelerated mice (SAM), specifically 3-month-old SAM resistant 1 (SAMR1) and SAM prone 8 (SAMP8) strains. Mice were distributed into four groups based on accelerated senescence and exercise status. Mice in the exercise groups exercised on a treadmill for 45 min a day, 3 days a week for 6 months.

Results: Exercise habit significantly increased BDNF expression and decreased the expression of p75 in both SAMR1 and SAMP8. Exercise also tended to decrease HDAC activity and significantly increased the activity balance of HAT to HDAC (HAT/HDAC) more greatly in SAMP8 than in SAMR1.

Conclusions: Therefore, the present study revealed that despite accelerated senescence, exercise habit up-regulated the expression of BDNF accompanying the decrease of the expression of p75, a receptor involved in apoptotic signaling. Furthermore, exercise habit increased HAT/HDAC specifically in aged mice, which might beneficially contribute to the transcriptional regulation for the degenerative changes in the hippocampus.

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OLFACTORY DYSFUNCTION IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

Taekyun Shin[1], Jeongtae Kim[1], Meejung Ahn[1], Yuna Choi[1]

1Department of Veterinary Anatomy, College of Veterinary Medicine, Jeju National University, Jeju Republic of Korea.

shint@jejunu.ac.kr

Aims. Olfactory dysfunction occurs is a common predisposing sign of central nervous system diseases including multiple sclerosis and its animal model of experimental autoimmune encephalomyelitis (EAE). The behavior and its underlying mechanism of olfactory dysfunction remains to be further discussed in the progression of EAE.

Methods. EAE was induced in C57BL/6 mice following immunization with myelin oligodendrocyte glycoprotein and adjuvant. The olfactory function was evaluated via the buried food test. The olfactory tissues were evaluated by next generation sequencing and by immunohistochemistry.

Results. On the buried food test, EAE-affected mice required significantly more time to find a bait pellet. Histopathology revealed that inflammation was identified in the olfactory bulbs of immunized mice with concurrent transient olfactory dysfunction. Analysis of differentially expressed genes (DEGs) in olfactory bulbs of EAE-affected mice revealed that genes of olfactory marker protein and stomatin-like 3 were significantly downregulated.

Conclusions. Summing up the results, olfactory dysfunction in EAE-affected mice is associated with primarily with initiation of inflammation in the olfactory bulbs of EAE mice, where downregulation of some olfactory signal transduction genes, particularly olfactory marker protein and stomatin-like 3, is important candidate molecules, leading to malfunction of olfaction in an animal model of human multiple sclerosis.

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DECISION-MAKING PROCESS IN AREAS OF SENSORY INTEGRATION

Goyri-Aguirre M[1]., Rojas-Hortelano, E[1]., and De Lafuente-Flores, V[1]

1Department of Neurobiology of Development and Neurophysiology, Institute of Neurobiology, UNAM Campus Juriquilla., Queretaro, Mexico

miriam@lafuentelab.org

Perceptual decision-making engages a variety of cognitive processes. In order to understand them, we need to study changes in neuronal activity patterns, related to the sensory representation of a stimulus, and to the execution of a behavioral response. Our main goal was to determine how sensory representations and decision-making activity are encoded.

We trained two Rhesus monkeys in a tactile categorization task were they actively reach and grasp an object to determine its spatial orientation. We recorded the activity of single neurons in the anterior intraparietal sulcus (AIP) during the execution of the tactile task.

Neuronal activity was clustered using a hierarchical algorithm and the resultant patterns were related to the temporal dynamics of the task. We found that different groups of neurons in the AIP responded to specific task events; such as movement, stimulus representation, and decision-making.

Our findings revealed that combined activity of these different neuronal populations converge in the decoding of the events of the task, representing faithfully the physical characteristics of somatosensory stimuli and encoding the behavioral choices.

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P362

AMOTL1: A NOVEL SYNAPTIC PROTEIN IMPORTANT FOR MICE SOCIAL BEHAVIOR AND THE BRAIN ORGANIZATION

Joanna Krzemień[1], Katarzyna Rojek[1], Maciej Winiarski[3], Paweł Boguszewski[2], Ewelina Knapska[3], Tomasz J. Prószyński[1]

[1] Laboratory of Synaptogenesis, Nencki Institute of Experimental Biology, Warsaw, Poland. [2]Laboratory of Animal Models, Nencki Institute of Experimental Biology, Warsaw, Poland. [3]Laboratory of Emotions Neurobiology, Nencki Institute of Experimental Biology, Warsaw, Poland

j.krzemien@nencki.gov.pl

Aims: Angiomotin family comprises of three scaffold proteins Amot, Amotl1 and Amotl2 that have been implicated in the regulation of cell polarity, migration and proliferation. Recent *in vitro* studies have reported that Amot localizes to the synapses in mature neurons and regulates dendritic spine maturation. We have found that Amot together with Yap1, the Hippo pathway transcription co-activator, are critical for proper dendritic arborization and mice locomotor coordination. However, to date the function of two other Angiomotins, Amotl1 and Amotl2 in neurons has not been investigated.

Methods: To study Amotl1 function in the mouse brain we generated systemic and neuron- specific knock-out (KO) mice. To assess general locomotion we performed an open field test. Amotl1 KO mice sociability was evaluated with the three-chamber task, automatic Eco-Hab approach and nesting test. To record animals anxiety response we used the marble burying test.

Results: In the present study we show that Amotl1 localizes to the synaptic compartments in neurons. Deletion of Amotl1 leads to hyperlocomotion, decreased anxiety-like behavior and alteration in mice sociability. Amotl1 ablation causes an increase in volume of lateral ventricles in the mouse brain by 50%. These features has been previously observed in animal models of various psychiatric disorders, such as schizophrenia or autism. Interestingly, mass spectrometry analysis of neuron-specific interactors demonstrated that Amotl1 binds to FMR1 and FXR1, mutations of which cause Fragile X syndrome.

Conclusions: We identified a novel synaptic protein Amotl1, the deletion of which causes behavioral deficits and that it could be a potential molecular target for the development of new therapeutics for neurological disorders.

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PROJECTIONS FROM NUCLEUS REUNIENS TO CA1 AFFECT EXTINCTION OF CONTEXTUAL FEAR MEMORY

Magdalena Ziolkowska[1], Anna Trabczynska[1], Małgorzata A. Śliwińska[2], Kacper Łukasiewicz[1], Magdalena Robacha[3], Malgorzata Borczyk[1],Agata Nowacka[1], Kasia Radwanska[1]

1Nencki Institute of Experimental Biology, Laboratory of Molecular Basis of Behavior, Warsaw, Poland;
2Nencki Institute of Experimental Biology, Laboratory of Imaging Tissue Structure and Function, Warsaw, Poland;
3Forschungzentrum Julich, INM-2, Julich, Germany

m.ziolkowska@nencki.gov.pl

Aim. In the current study we investigated the contribution of the area CA1 of the dorsal hippocampus and projections from nucleus reuniens (RE) to this region in extinction of contextual fear memory. The function of these regions in memory formation is well documented, however, their contribution to memory extinction is still speculative.

Methods. To test the role of dorsal CA1 and projections from RE in fear memory extinction we used AAV2/9 encoding DREADD synapsin-hM4Di-mCherry, which inhibits cell activity upon stimulation with CNO. C57BL/6 mice were transfected with AAV2/9 into the CA1 area of the dorsal hippocampus and two weeks after stereotactic surgery, mice underwent contextual fear conditioning, fear extinction session and test session.

Results. Inhibition of CA1 piramidal cells with DREADD-CNO system during extinction session prevented consolidation of fear memory extinction, indicating that dorsal area CA1 contributes to fear memory extinction. We observed that fear memory extinction resulted in decreased density of dendritic spines containing PSD95 (PSD+) in the stratum oriens (stOri) and increased density of PSD+ dendritic spines in the stratum lacunosum moleculare (stLM) of CA1 principal neurons, indicating that synaptic input to stOri is weakened in contrary to stLM in which it is enhanced during fear memory extinction. Since one of the important inputs to stLM of CA1 is nucleus reuniens (RE), in the following step we tested the function of RE in our model.

Conclusions. Chemogenetic inhibition of nucleus reuniens (RE) promotes fear memory attenuation and down-regulation of PSD-95 in the CA1 area.

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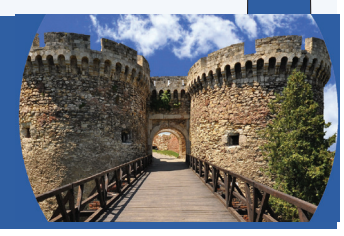

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INFLUENCE OF MATERNAL IMMUNE ACTIVATION DURING MID-PREGNANCY ON LEARNING ABILITY AND PERSEVERATIVE BEHAVIORS OF LAMBS (OVIS ARIES)

Florek W[1], Barłowska K[1], Nowak R[2], Modliński JA[1], Sampino S[1]

1Institute of Genetics and Animal Breeding of the Polish Academy of Sciences, Jastrzębiec, Magdalenka, Poland;
2PRC, INRA, CNRS, IFCE, Université de Tours, Nouzilly, France

w.florek@ighz.pl

Maternal infection during pregnancy is associated with an increased risk of neurodevelopmental disorders in offspring. A variety of rodent models of Maternal Immune Activation (MIA) have been developed in last decades. However, there are limitations in relying solely on rodent models to study complex human brain disorders. The aim of the present study was to establish a new translational model of MIA evoked by lipopolysaccharide (LPS) administration in pregnant sheep.

Pregnant ewes were injected with LPS (MIA, n=12) or saline solution (SAL, n=12) at 85th day post coitum. At the age of 40 days, lambs were subjected to the V-detour test, designed to examine learning abilities, cognitive flexibility and perseverative behaviors, using a position habit acquisition training followed by reversal learning.

LPS influenced the ability of male lambs to achieve reversal learning, although difference between groups was not significant (Chi square test, $p=0.0719$). Moreover, while control lambs improved significantly their detour performances comparing the first with the last trials ($p<0.001$, 1-way ANOVA), MIA lambs did not ($p>0.05$). LPS administration did not affected the occurrence of perseverative behaviors.

The obtained results indicate that a single administration of LPS during mid-pregnancy does not affect perseverative behaviors, although it influences learning and cognitive flexibility. Our data suggest that male individuals may be more susceptible to MIA than females. Further studies should consider a chronic LPS treatment instead than a single injection, to better model human infection.

This study was supported by KNOW Leading National Centre Scientific Consortium “Healthy Animal-Safe Food” (grant no. KNOW2015/CB/PRO1/47).

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DEPRESSIVE VULNERABILITY AND PERSONALITY TRAITS IN ALZHEIMER'S DISEASE

Joana Henriques-Calado[1,2], Maria Eugénia Duarte-Silva[1]

1Faculdade de Psicologia, Universidade de Lisboa, Lisboa, Portugal. 2CICPSI, Faculdade de Psicologia, Universidade de Lisboa, Lisboa, Portugal

joanahenriquescalado@gmail.com

Aims. This research is geared towards the evaluation of current and pre-morbid depressive vulnerability dimensions in Alzheimer's disease. The depressive developmental perspective and the Five-Factor Model of Personality were taken as references.

Methods. The study was conducted with two groups. Current measure: Alzheimer's disease Group, consisting of 44 female participants (M Age = 81.36 years); Pre-morbid measure: Alzheimer's disease Group Informants (n = 40). Self-reported assessment, in the form of individual interview sessions: Depressive Experiences Questionnaire and NEO Five-Factor Inventory. Four multiple linear regressions were computed.

Results. Self-Criticism depressive vulnerability is a general indicator of psychopathology. In pre-morbidity, Neuroticism (β = .41), Agreeableness (β = -.63) and Conscientiousness (β = -.08) predicted Self-Criticism, explaining 64% of the variance. In terms of current personality, Extraversion (β = .22), Openness (β = .45) and Agreeableness (β = -.23) predicted Self-Criticism, explaining 38% of the variance.

Conclusions. These findings are relevant to research relating depressive vulnerability to personality traits and psychopathology in Alzheimer's disease.

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PUPIL RESPONSES SUGGEST REDUCED NORADRENERGIC ACTIVATION AND IMPAIRED UNCERTAINTY REPRESENTATION IN OLDER ADULTS

Maria J. Ribeiro[1], [2] and Miguel Castelo-Branco[1]

1CIBIT, ICNAS, CNC.IBILI, University of Coimbra, Coimbra, Portugal. 2iCBR, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

mjribeiro@fmed.uc.pt

Our aim was to investigate if ageing affects the modulation of arousal. Impairments in the ability to modulate arousal in older adults might explain difficulties in the performance of tasks requiring fast reactions. Importantly, age-related differences in arousal modulation would reflect changes in the noradrenergic system, which is important in the maintenance of brain health in old age.

We investigated task-related modulation of arousal levels by measuring changes in pupil size under constant illumination conditions, in humans. We studied task-related pupil responses in auditory cued reaction time tasks, in 36 young adults (mean age = 23 years)

Pupil responses scaled with reaction time in within-subject analyses. Slower reaction times were associated with larger pupils after the motor responses. As slower reactions are associated with uncertainty in the accuracy of the decision, larger pupils appear to indicate increased arousal levels related with the processing of response uncertainty. Notably, this modulation of pupil size with uncertainty was significantly reduced in older adults. In this group, the task-related pupillary responses were less sustained, returning sooner to baseline, especially after slow reactions.

These results indicate reduced activation of the noradrenergic system during periods of response uncertainty in older adults. This impairment in noradrenergic activation might affect the ability to update task representations and learn from errors and might represent a relevant feature of ageing of the brain.

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CONVERGENCE OF REWARD AND AVERSION PROCESSING IN NUCLEUS ACCUMBENS MEDIUM SPINY NEURON SUBTYPES

Carina Soares-Cunha[1,2], Nivaldo Vasconcelos[1,2,3], Bárbara Coimbra[1,2], Ana Verónica

1Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal;
2ICVS/3B's-PT Government Associate Laboratory, Braga/Guimarães, Portugal;
3Departamento de Física, Universidade Federal de Pernambuco, Pernambuco, Brazil;
4Clinical Academic Center-Braga (2CA), Braga, Portugal

carinacunha@med.uminho.pt

Reward is as important as aversion for survival. Deficits in decoding rewarding/aversive signals are present in several neuropsychiatric disorders, such as depression or addiction, since the brain reward circuit is often impaired. The reward circuit, comprising projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) is crucial for reward/aversion processing.

Aim: Though the dominant view on the field postulates that NAc D1-expressing medium spiny neurons (D1-MSNs) convey reward, while D2-expressing MSNs (D2-MSNs) encode aversion, recent results challenged this view. Thus, in this study we aim to better understand the role of NAc D1- and D2-MSNs in reward and aversion.

Results: In the present study we show that both MSN populations can drive reward and aversion, depending on their pattern of activation. These opposite behaviors result from differential electrophysiological patterns in downstream targets, namely the ventral pallidum (VP) and VTA. Brief MSN optogenetic stimulation of either D1- or D2-MSNs elicited positive reinforcement, in line with the observed decreased VP-to-VTA inhibitory tone, and increased VTA dopaminergic activity. Prolonged activation of either MSN population drove aversion, with distinct electrophysiological effects. Interestingly, we show that distinct patterns of neuronal activation involve different neurochemical signals, namely dopaminergic and opioidergic, and that differentially influence cocaine-induced place preference.

Conclusion: we show that D1- and D2-MSNs bi-directionally control reward/aversion, highlighting the complexity of this system.

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DISTINCT ROLES OF BETA AND GAMMA OSCILLATIONS DURING INTEGRATION OF AMBIGUOUS MOTION

Gabriel Nascimento Costa[1,2], Michael Schaum[3], Ricardo Martins[1,2], João Valente Duarte[1,2], João Castelhano[1,2], Michael Wibral[3], Miguel Castelo-Branco[1,2]

[1]Coimbra Institute for Biomedical Imaging and Translational Research (CIBIT), University of Coimbra, Coimbra, Portugal. [2]Institute of Nuclear Sciences Applied to Health (ICNAS), University of Coimbra, Coimbra, Portugal.. [3]MEG Unit, Brain Imaging Center, Johann Wolfgang Goethe University, Frankfurt am Main, Germany

gcosta18@gmail.com

The visual brain is constantly challenged with interpreting unclear and ambiguous visual scenes. When interpreting visual motion, the brain is required to decide whether to integrate distinct motion cues that may correspond to a global pattern moving in a direction distinct from its components. How the visual brain integrates information processed in distributed regions is an unresolved issue in neurosciences. Moreover, in situations of ambiguity the brain is clearly capable of interpreting motion in distinct, even opposing, directions, raising the question of what drives the decision to perceive one way or another.

Here we studied perception of motion requiring visual integration/binding across the visual hemifields. A task requiring participants to report the perceived configuration of a moving stimulus that could be perceived in either a “bound” (one integrated surface) or an “unbound” (two objects separated, one in each hemifield) configuration was carried out while Magnetoencephalography (MEG) data was recorded. Motion stimuli were presented either in an ambiguous, i.e. physically constant, or an unambiguous fashion, i.e. with clear cues of motion direction.

Perception of the bound configuration was predominant and was associated with increased beta activity (12-22 Hz) found mainly over parietal areas. On the other hand, gamma oscillations (55-95 Hz) were observed over occipital regions and increased when the unbound configuration, i.e. the less frequent percept, was perceived. These differences were not observed when the same percepts resulted from an unambiguous stimulus. Thus, visual experience seems to be guided by distinct oscillations acting over different brain regions.

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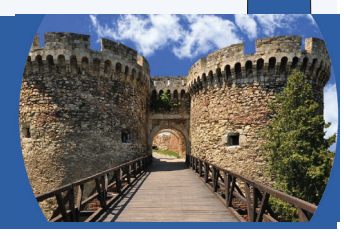

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RESEARCH – FROM CELL TO THE WHOLE SYSTEM. THE NEED FOR BEHAVIORAL STUDIES IN ANIMALS.

Ianis Kevyn Stefan Boboc[1], Andrei Gresita[2], Victor Gheorman[2], Maria Brosteanu[2], Tudor Adrian Balseanu[2], Bogdan Catalin[2], Maria Bogdan[1]

1Faculty of Pharmacy, University of Medicine and Pharmacy, Craiova, Romania. 2Faculty of Medicine, University of Medicine and Pharmacy, Craiova, Romania

kevynboboc@gmail.com

Aim: Depression represents a major complication of stroke, with up to 30% of all patients needing antidepressant medication. Trazodone is a well known antidepressant that has been reported to have a neuroprotective effect. In this study we wanted to test the clinical outcome of different aged mice treated with trazodone after experimental stroke.

Methods: Young (3-5 months, n=26), old (18-24 months, n=17) and control (3-5 months, n=6) C57BL/6 females mice were intraperitoneally injected with 36 mg trazodone hydrochloride/kg for 28 days after focal stroke. Motor recovery was quantified by beam walk test and adhesive tape removal test, while the depressive status of the animal was assessed using the hole board test. This tests were performed at a two day interval.

Results: Functional testing showed mostly random differences between groups, with no clear benefit of trazodone treatment. It might be possible that the previously reported neuroprotective effect of trazodone was not significant enough due to the slightly lower dose used in the present study, in order to prevent side effects. The only notable differences were in beam walk test and adhesive removal test between old and young animals showing that proper behaviour analysis should be also aged matched.

Conclusion: We were not able to identify any improvement in motor recovery after stroke during trazodone treatment.

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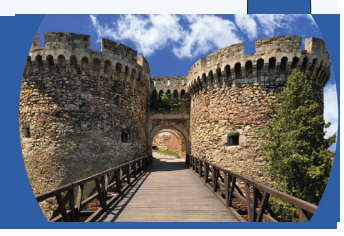

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POSTER SESSION 3

P371

KAINIC ACID APPLICATION ON THE CEREBELLAR HEMISPHERE INDUCES SPECIFIC DYSTONIC PHENOTYPES IN MICE

Vanhaeren Sebastien Gérard[1], Elena Laura Georgescu[1], Ioana Antoaneta Georgescu[1], Denise CM Zahiu[1], Alexandru Şteopoaie[1], Ţîrlea Ştefan Alexandru[1], Adrian Pana[1], Ana-Maria Zagrean[1], Mădălina Popescu[1], Daniela Popa[1,2]

1Division of Physiology and Fundamental Neuroscience, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania. 2Institut de Biologie de l'Ecole Normale Supérieure, INSERM U1024, CNRS UMR8197, Paris, France

sebi.vanhaeren@yahoo.com

Our study aim was to evaluate the role of cerebellum in dystonia, a debilitating motor disorder.

Methods: Low doses of kainic acid were injected into the left cerebellar cortex or into the vermis, for five consecutive days, in mice. We recorded a baseline behavior for each mouse and then we performed video tracking recordings for the next five days that monitored the activity both 10 min prior and 90 minutes after the daily microinjection. The average amount of time for active wake and quiet wake was calculated and the dystonic postures or movements were assessed.

Results: The kainate microinjections into the left cerebellar cortex induced especially ipsilateral dystonic contractions whereas vermis microinjections induced a generalized dystonia. The dystonia scores gradually reduced during the final 3 days. We observed a decrease in mice motor activity, during the baseline recordings, in the first 3 days of kainate administration into the left cerebellar hemisphere, followed by an incremental trend in days 4 and 5. The recordings of post-kainate state, however, showed reduced motor activity to the baseline in day 1, 2 and 3 followed by increasing values in day 4 and day 5. These changes suggest a possible compensatory mechanism.

Conclusions: The cerebellar kainic acid administration on the cerebellar hemisphere induces lateralized dystonic phenotypes. The behavioral changes observed in our mouse model of repetitive dystonia suggest the development of a compensatory mechanisms in the cerebello-basal ganglia-cortical network, within days.

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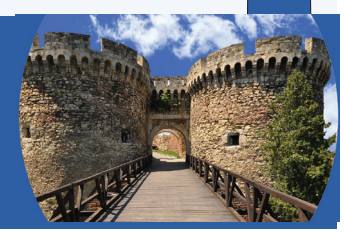

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P372

OXYTOCIN REDUCES HIPPOCAMPAL INJURY AND SEIZURES INDUCED BY THE PERINATAL ASPHYXIA

Pavel Bogdan [1], Panaitescu Anca Maria [1, 2], Isac Sebastian [1], Nikolaos Zygouropoulos [1], Ilie Andrei Sorin [3], Ceanga Mihai [4], Zagrean Leon [1], Peltecu Gheorghe [2], Zagrean Ana-Maria [1]

1Physiology and Neuroscience Division, "Carol Davila" University of Medicine and Pharmacy, Bucharest Romania. 2Obstetrics and Gynecology Department, Filantropia Hospital "Carol Davila" University of Medicine and Pharmacy, Bucharest Romania. 3Department of Pharmacology, University of Oxford, Oxford, United Kingdom of Great Britain and Northern Ireland. 4"Hans Berger" Department of Neurology, Jena University Hospital, Jena, Germany

bogdan.pavel@umfcd.ro

Aims. Foetal asphyxia triggers neuronal damage, uncontrolled seizure activity and long-term neurological deficits. Oxytocin is known to modulate the immature brain's excitability with neuroprotective effect. This study investigates the effect of exogenous oxytocin on acute brain injury and seizure burden in a perinatal model of asphyxia in rats.

Methods. Asphyxia was obtained by exposing immature rats for 90 minutes to 9% O2 and 20% CO2. Control rats were kept in ambient room-air for the same time interval. Oxytocin (0.02 UI/g body weight, dissolved in saline solution) or vehicle alone were nasally administered 30 minutes before the asphyxia episode, for oxytocin or control groups, respectively. Seizure burden was assessed by the cumulative number of loss of righting reflex (LRR) over a two-hour post-asphyxia period. Acute brain injury was assessed 24-hours after exposure through hippocampal S-100 beta, a biomarker of cellular injury.

Results. Asphyxia increased both LRR and hippocampal S-100 beta protein compared to controls, and these effects were significantly reduced by oxytocin administration.

Conclusions. Oxytocin administration before asphyxia exposure reduce both seizure burden and hippocampal injury in rats, supporting a potential neuroprotective role for oxytocin in perinatal asphyxia.

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P373

THE EFFECTS OF 5-HT2A RECEPTOR CHRONIC ACTIVATION ON THE BEHAVIOR AND THE BDNF SYSTEM OF C57BL6/J MICE

T.V. Ilchibaeva, A.S. Tsybko, E.A. Filimonova, N.K. Popova

Department of Behavioral Neurogenomics, the Federal Research Center Institute of Cytology and Genetics SB RAS, Novosibirsk, Russia

rbicehok@mail.ru

The effects of 5-HT2A receptor chronic activation with mixed 5-HT2A/2C receptor agonist DOI, selective agonists TCB-2 and 25CN-NBOH on the behavior and the BDNF system were investigated.

Expression of BDNF, TrkB and p75NTR receptors was assessed by real-time RT-PCR and western-blot analysis. The Morris water maze was used to test spatial learning and memory.

Chronic treatment with TCB-2 and 25CN-NBOH (1 mg/kg, i.p., 14 days) markedly decreased the escape latency in the water maze. 25CN-NBOH also significantly decreased the total distance to platform. Significant desensitization of the 5-HT2A receptors was found after all utilized agonists.

Considerable changes of BDNF, TrkB and p75NTR receptors expression were shown after 5-HT2A receptor chronic activation. Both TCB-2 and 25CN-NBOH markedly increased the BDNF mRNA level in the hippocampus (Hc) and striatum (St). TrkB mRNA level was reduced after 25CN-NBOH in the midbrain (Mb) and was elevated after TCB-2 in St. In the frontal cortex (Fc) TCB-2 decreased the p75NTR mRNA level, while 25CN-NBOH increased it in Hc. It was found, that all agonists elevated the proBDNF protein level in Fc, but DOI and 25CN-NBOH also increased it in Mb. TrkB protein level was decreased after all agonists in Mb, while it was reduced in St only after TCB-2. Both TCB-2 and 25CN-NBOH increased the p75NTR protein level in St.

Thus, considerable effects of the chronic activation of the 5-HT2A receptors on spatial learning as well as on the BDNF system were shown for the first time.

The work supported by the RSF (#17-15-01021).

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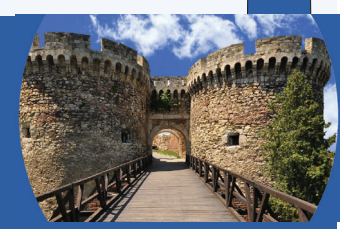

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EFFECTS OF THE TYPE OF IMMUNOTOXIN 192IGG-SAPORIN ADMINISTRATION ON THE BEHAVIOR AND NEURODEGENERATION IN THE HIPPOCAMPUS.

Dobryakova Y.V., Bolshakov A.P., Stepanichev M.Y., Zaichenko M.I., Gulyaeva N.V., Markevich V.A.

Institute of Higher Nervous Activity and Neurophysiology of RAS, Moscow, Russia

julkadobr@gmail.com

Aims: Cholinergic system plays an important role in cognition and loss of cholinergic neurons may contribute to the development of Alzheimer's disease. We used a conjugate of antibody to p75/NFGR receptor with saporin (192IgG-saporin), to induce the cholinergic deficit in the hippocampus.

Methods and results: We compared effects of intracerebroventricular (i.c.v.) and intraseptal injection of 192IgG-saporin on the learning performance and cholinergic neurodegeneration. Behavioral testing began 3 weeks after the injection. In Morris Water Maze, i.c.v. injected rats had longer latencies to reach the platform and higher distance swam compared to control. Rats treated intraseptally had no behavioral deficits in the Morris Water Maze. In the beam walking test both groups showed significant reduction of motor performance. Locomotor and exploratory activity in the open field task was affected only by intraseptal toxin administration as compared to the control. Analysis of the ChAT stained sections showed that both types of administration led to a similar loss of ChAT-positive neurons in septal area. The assessment of neurodegeneration with Nissl-stained sections of the hippocampus after i.c.v and intraseptal injection did not show the same picture. The number of neurons in the CA3 area after i.c.v. administration was significantly low as compared to septal injection.

Conclusion: Our data suggest that different types of saporin administration lead to different disturbances in behavior that can be associated with neurodegeneration in hippocampus.

The work was supported by Russian Science Foundation No 16-15-10403П.

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DIFFERENTIAL PHOSPHORYLATION OF MITOCHONDRIAL GLUCOCORTICOID RECEPTOR IN BRAIN REGIONS OF FEMALE AND MALE RATS IN NEUROINFLAMMATORY MODEL OF DEPRESSION

Zeljka Brkic[1], Zorica Petrovic[1], Emilija Glavonic[1], Minja Milosavljevic[1], Ester Francija[1], Iva Lukic[1], Milos Mitic[1] and Miroslav Adzic[1]

1Department of Molecular Biology and Endocrinology, VINCA Institute of Nuclear Sciences, University of Belgrade, Serbia

brkic.zeljka89@gmail.com

Mitochondrial dysfunction can result from the interplay between elevated inflammation and alterations in hypothalamic–pituitary–adrenal (HPA) axis, and could contribute to pathogenesis of depression. Here we investigated the effects of lipopolysaccharide (LPS) on phosphorylation and transcriptional activity of mitochondrial glucocorticoid receptor (GR) in prefrontal cortex (PFC) and hippocampus of female and male rats with depressive-like behavior.

We followed the effects of 7-day LPS treatment (500 μg/kg) on the behavior and the activity of HPA axis. We also followed the alterations in mitochondrial levels of GR, pGR-232 and pGR-246, and the mRNA levels of two mitochondrial-encoded subunits of cytochrome C oxidase regulated by GR, COX-1 and COX-3, in PFC and hippocampus of female and male rats.

LPS induced depressive-like symptoms and stimulated HPA axis in both sexes. However, the treatment affected GR and the expression of GR-regulated genes in both structures differently in males and females. In PFC, the treatment reduced the levels of total GR and pGR-246, and elevated mRNA levels of both genes only in males, while in hippocampus altered levels of total GR and its phosphoforms were followed by decreased gene expression only in females.

Although LPS caused depressive-like symptoms and stimulated HPA axis in both sexes, it affected mitochondrial GR and expression of cytochrome c oxidase subunits differently in both structures in males and females. These results suggest that tissue differences in brain metabolism after LPS are sex-specific, and could be associated with alterations in mitochondrial GR levels and its phosphorylation.

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STATE RELATED SLEEP SPINDLE DYNAMICS IN THE HEMIPARKINSONIAN RAT

Jelena Ciric, Jelena Petrovic, Jasna Saponjic
University of Belgrade, Department of Neurobiology, Institute for Biological Research - Sinisa Stankovic, Belgrade, Serbia
jelena.ciric@ibiss.bg.ac.rs

Aims: We followed the impact of unilateral substantia nigra pars compacta (SNpc) lesion on the cortical and hippocampal sleep spindle (SS) and high voltage sleep spindle (HVS) dynamics during NREM and REM sleep.

Methods: We performed the experiments in 33 adult Wistar rats. During operative procedure for the EEG and EMG electrodes implantation, the SNpc lesion was done by microinfusions of 6-OHDA. Spontaneous sleep was recorded during 6h at 14 and 42 days following operation. After conventional amplification and filtering, the analog signals were digitized (256/s). We differentiated NREM and REM 10s epochs, based on EEG of the motor cortex (MCx) and hippocampus (Hipp) and EMG. SS and HVS identification and extraction was done by automatic detection with visual validation.

Results: SS are the hallmarks of NREM sleep, but they also occur during REM sleep in the MCx and Hipp of the control rats. SS are always longer in REM vs. NREM sleep in both structures, and consistently slower in the Hipp ($p \leq 0.05$). The SNpc lesion increased the density of SS in both structures and shortened them in the MCx during NREM sleep ($p \leq 0.05$).

HVS are the hallmarks of REM sleep in the control rats, slower in the Hipp vs. MCx ($p=0.02$), and the SNpc lesion increased their density in the MCx, but shortened them more consistently in the Hipp during REM sleep ($p \leq 0.03$). The SNpc lesion did not change the SS/HVS intrinsic frequency ($p \geq 0.19$).

Conclusions: We demonstrated an importance of SNpc dopaminergic innervation in the SS/HVS dynamics control.

Acknowledgement: This work was supported by Serbian Ministry of Education, Science and Technological Development Grant OI 173022.

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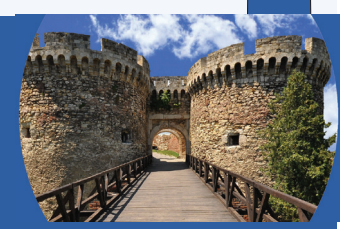

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FEAR EXTINCTION DEFICITS IN ADOLESCENT MALES CAN BE RESCUED BY PROLONGED EXTINCTION TRAINING

Emilija Glavonic[1], Zorica Petrovic[1], Ester Francija[1], Milos Mitic[1], Zeljka Brkic[1], Minja Milosavljevic[1] and Miroslav Adzic[1]

1Department of Molecular Biology and Endocrinology, VINCA Institute of Nuclear Sciences, University of Belgrade, Serbia

eglavonic@gmail.com

Fear extinction is a form of associative learning crucial for attenuation of fear responses learned through fear conditioning. Perturbations of these processes can result in development of psychopathologies. Adolescence is a developmental stage when the incidence of psychiatric disorders peaks. Additionally, functioning of neural circuits involved in fear-related learning is influenced by sex hormones. Therefore, our aim was to investigate potential disturbances of fear conditioning and extinction in adolescents of both sexes, and to ascertain whether prolonged extinction training could mitigate possible deficits.

We examined animals' acquisition of fear and its extinction using a cued conditioning paradigm. Experimental groups were subjected to fear conditioning followed by four or seven days of extinction training. We measured acquisition of fear, extinction efficiency and recovery of fear responses over time.

Behavioral analyses revealed uniform fear acquisition across all groups. On the other hand, adolescent males exhibited recovery of fear responses and attenuated extinction learning across four days when compared to adults, and this deficiency was resolved with three additional extinction sessions. Females showed successful extinction learning regardless of their age.

Disturbed patterns of extinction learning in adolescent males are not a result of differential fear acquisition, but arise due to lack of extinction memory consolidation or its retention and can be rescued by prolonged extinction training. Concurrently, absence of fear extinction deficits in females implicates their sex hormones as positive modulators of this process. Altogether, observed behavioral data outline adolescence as a vulnerable period for developing fear-related disorders in a sex-specific manner.

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SMARTFONES – AN EEG ENABLED HEADPHONES FOR OUTSIDE-OF-LAB COGNITIVE EXPERIMENTS

Aneta Kartali, Ivan Gligorijević, Pavle Mijović, Bogdan Mijović
mBrainTrain LLC, Belgrade, Serbia

ivan@mbraintrain.com

Professional mobile EEG systems are rather novel and powerful tool that enable high-end research outside laboratory conditions.

Since recently, there have been attempts to use so-called concealed EEG. Printed electrodes placed around the ears, termed cEEGrids have been successfully applied to that end. However, there are also several drawbacks, such as stable electrode placement and the fact that a headband is still needed to hold the EEG amplifier.

Building on top of the cEEGrid concept, we introduce a new device, Smartfones, an EEG enabled headphones. They are easy to mount and perfectly conceal the original intent to measure EEG in a consumer accepted wearable – headphones.

On top of concealing EEG, Smartfones integrate ability to play sounds and music. We test the resulting concept in the known three-tone auditory oddball paradigm.

We demonstrate the ability to observe auditory ERPs in mobile and seated conditions as a first introductory step to this new modality of EEG recordings.

Subjects are often instructed to pay attention to visual or auditory stimuli in presence of real-world interruptions that are treated as physiological noise. Large part of that physiological noise stems from the fact that outsiders are "attracted" by the EEG cap that subjects are wearing which consequently leads these subjects to point their attention to these outside observers. This can further raise an issue of validity of a desired experiment.With the concept of concealed EEG, integrated in headphones, we mitigate this problem and demonstrate the ability to conduct complex outside-of-lab cognitive experiments.

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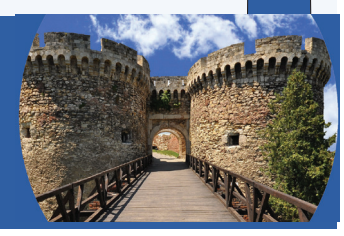

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ASSOCIATION OF GLUCOCORTICOID RECEPTOR ALPHA ISOFORMS WITH DEPRESSIVE SYMPTOMS IN MICE OF BOTH SEXES

Minja Milosavljević, Zorica Petrović, Željka Brkić, Ester Francija, Emilija Glavonić, Miloš Mitić, and Miroslav Adžić

Department of Molecular Biology and Endocrinology, VINCA Institute of Nuclear Sciences, University of Belgrade, Belgrade, Serbia.

minjamil@vin.bg.ac.rs

Stress exposure during adolescence has been correlated with an increased risk of depressive and anxiety disorders. Although majority of studies investigate the role of full length 95kDa GR in the pathophysiology of psychiatric disorders, recent research indicated GR alpha translational isoforms (67, 50, 40, 25kDa) abnormalities. The aim of our study was to reveal the association of hippocampal GR alpha isoforms with depressive phenotype in both sexes.

We exposed adolescent male and female C57BL/6J mice to chronic unpredictable stress (CUS) for 12 days starting at postnatal day 28 (PND28). We measured behaviour at PND70 with open field, elevated plus maze and novelty suppressed feeding tests. Levels of GR alpha isoforms in hippocampal nucleosol and cytosol were measured by Western blot. Group differences were determined by General Linear Model.

Adolescence stress exposure increased anxiety- and depressive-like behaviour in mice of both sexes. Although we didn't find alterations in full length GR alpha in either of sexes, we detected sex-specific alterations in several GR alpha isoforms. In females, we found nuclear translocation of GR 40kDa while the levels of GR 50, 25kDa were decreased in both cellular compartments. As for males, increased levels of nuclear GR 40, 25kDa isoforms were found.

Results suggested that adult mice of both sexes exhibited depressive-like behaviour after CUS which is associated with nuclear translocation of GR 40kDa isoform in both sexes. Alterations of other GR alpha isoforms were sex specific. These findings provide the first evidence of GR alpha isoforms abnormalities in experimental model of depression.

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THE INFLUENCE OF PROPOFOL ANESTHESIA EXPOSURE ON MOTIVATION/HEDONIC BEHAVIOR IN PERIPUBERTAL RATS

Pavković Ž, Potrebić M, Kanazir S, Pešić V

Department of Neurobiology, Institute for Biological Research "Siniša Stanković", University of Belgrade, Belgrade, Serbia

zeljko.pavkovic@ibiss.bg.ac.rs

Aims: Adolescence is characterized by heightened vulnerability to environmental factors and neuroactive drugs. Considering addictive potential of propofol we aimed to examine motivation/hedonic behavior after propofol anesthesia exposure (PAE) in peripubertal rats as the rodent model of periadolescence.

Methods: Male Wistar rats 35 ± 1 day old were used. After body weight (BW) measurement and appropriate injection (controls: 0.9% NaCl, i.p.; PAE: 75 mg/kg, i.p.) each rat was placed in a clean cage with bedding and subjected to sucrose preference test (SPT; two-bottle choice: water/1% sucrose solution or water/20% sucrose solution) with free access to standard chow. Measurements (BW along with food, water and sucrose consumed) were done for 24 h periods for 4 consecutive days, with switched position of bottles.

Results: In the SPT with 1% sucrose solution PAE animals showed no changes in sucrose consumption/preference (measure of consummatory anhedonia) but ate less amount of food and had less BW gain compared to the control. In contrast to the control, PAE animals showed strong preference to 20% sucrose solution and consumed the same amount of food as control animals.

Conclusions: In peripubertal rats, PAE produces transient motivational deficit in goal directed actions such is regular feeding without changing hedonic behavior. In permissive environment it promotes preference to novel/intense stimulus, recovering motivation deficiency. These findings accentuate the importance of environmental stability for PAE-related post-anesthesia recovery and are of clinical significance, emphasizing the necessity of clinical research focused on this concept.

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P381

CORTICAL AND HIPPOCAMPAL SLEEP IN DIFFERENT EXPERIMENTAL MODELS OF PARKINSON'S DISEASE

Jelena Petrovic, Jelena Ciric, Jasna Saponjic

University of Belgrade, Department of Neurobiology, Institute for Biological Research - Sinisa Stankovic, Belgrade, Serbia

jelena.petrovic@ibiss.bg.ac.rs

Aims: We investigated the alterations of cortical and hippocampal sleep, locomotor activity and spatial memory abilities in the hemiparkinsonian rats with or without cholinopathy.

Methods: We performed the experiments in adult male Wistar rats chronically implanted for sleep recording in four experimental groups: the controls, bilaterally pedunculopontine tegmental nucleus (PPT) lesioned rats (Parkinson's disease (PD) cholinopathy), the substantia nigra pars compacta (SNpc) lesioned rats (hemiparkinsonism), and the rats with a combined unilateral SNpc/bilateral PPT lesion (hemiparkinsonism with cholinopathy). We recorded sleep for 6h and differentiated Wake/NREM/REM 10s epochs based on EEG from the motor cortex or hippocampus and EMG.

Results: Although PD cholinopathy did not change sleep/wake states architecture ($p \geq 0.40$), both groups of the hemiparkinsonian rats demonstrated prolonged Wake duration ($p=0.01$), without change of NREM/REM duration ($p \geq 0.13$). Conversely to the hippocampal Wake gamma and NREM delta augmentation after the PPT lesion ($p \leq 0.01$), the cortical and hippocampal theta amplitude was augmented across all sleep/wake states ($p \leq 0.01$) in both groups of the hemiparkinsonian rats, and it was followed by an attenuated cortical Wake/NREM delta and augmented NREM sigma in the SNpc lesioned rats ($p \leq 0.01$), or by the cortico/hippocampal Wake delta and cortical REM beta attenuation ($p \leq 0.01$) in the SNpc/PPT lesioned rats. There was no alteration of locomotor activity in all experimental groups ($p \geq 0.37$), but no reduction in locomotion during habituation ($p \geq 0.11$) indicated impaired spatial memory abilities in both groups of the hemiparkinsonian rats.

Conclusions: The SNpc dopaminergic control is important in sleep regulation, theta rhythm generation and spatial memory abilities.

Acknowledgement: This work was supported by the Serbian Ministry of Education, Science and Technological Development Grant OI 173022.

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P382

THE EVOLUTION OF BEHAVIORAL EXPRESSIONS TO SOCIAL ISOLATION IN EARLY ADOLESCENCE

Milica Potrebić, Željko Pavković, Selma Kanazir, Vesna Pešić
Department of Neurobiology, Institute for Biological Research "Siniša Stanković", University of Belgrade, Belgrade, Serbia
milica.potrebic@ibiss.bg.ac.rs

Aims: The potential for peer rejection proliferate in modern/urban societies. A desire to feel socially accepted becomes particularly intense during early adolescence and peer rejection during this period has been approved as a risk factor for an increase in depressive-like symptoms in both genders. We aimed to examine the evolution of behavioral expressions to social isolationin early-to-mid adolescence, using peripubertal rats as the rodent model of periadolescence.

Methods: Male Wistar rats 29 postnatal days (P) old were used as in rats a peak interval of social development is P30-35. The animals from 8 litters (5 males per litter/cage) were weighed, subjected to exploratory activity monitoring and randomly selected for group (GH; n=3 per cage) or single housing (SH; n=2 cages) at P29, and left undisturbed with free access to food and water. At P36 (mid-adolescence onset) they were subjected to weighing and exploratory activity monitoring; at P43 (mid-adolescence ending) response to d-amphetamine (dopamine releaser) was monitored after intra-session habituation.

Results: After 7 days of isolation, exploratory behavior of SH animals compared to GH was increased without anxiety signs; after 14 days of isolation, control-like exploratory response to novel environment was observed along with strong decrease in d-amphetamine induced locomotion and stereotypy (not rearing). Body weights of GH and SH animals were highly similar.

Conclusions: An increase in exploratory activity without anxiety is the first manifestation of social isolation started in early adolescence, with the behavioral manifestations of impaired mesolimbic dopaminergic transmission being evident at the end of mid-adolescence and only in response to d-amphetamine.

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EFFECTS OF ENHANCED ACTIVATION OF ALPHA 5 CONTAINING GABAA RECEPTORS ON LEARNING AND MEMORY

Anja Santrač[1], Tamara Timić Stamenić[2], Bojan Batinić[3], Branka Divović Matović[1], Tamara Stanković[1], Michael Poe[4], James Cook[4], Miroslav Savić[1]

1Department of Pharmacology, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia. 2SOM-Anesthesiology, Anschutz Medical Campus, University of Colorado Denver, Denver- Colorado, USA. 3Department of Physiology, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia. 4Department of Chemistry and Biochemistry, University of Wisconsin-Milwaukee, Milwaukee- Wisconsin, USA.

anjasan@pharmacy.bg.ac.rs

Aims: Research showed that deactivation of alpha5-containing GABAA receptors (alpha5GABAARs) improves learning and memory, but recently, enhanced activation of these receptors has been recognized as a potential treatment of cognitive impairments in dementia and schizophrenia. Our aim was to test our previously published alpha5GABAARs positive modulator, MP-III-022, in cognitive tests.

Methods: We performed short-term memory (30 min) tests: social novelty discrimination (SND) and novel object recognition (NORT); and long-term memory tests: Morris water maze (MWM), NORT and SND (24 h). Rats were given i.p. solvent (SOL), 1, 2.5 or 10 mg/kg of MP-III-022 (MP1, MP2.5, MP10) 20 min before the start of the experiment. For MWM, NORT24 and SND24, they were treated each day, the last two tests with only one dose: SOL-SOL, SOL-MP1, MP1-SOL, MP1-MP1.

Results: In SND and NORT, only MP10 group improved the memory of rats. Concerning the long-term memory in MWM, MP10 worsened the overall performance of animals, while MP1 improved it, especially on the second day. Thus, we decided to run NORT24 and SND24 only with MP1, and showed that, when animals received two doses of MP1, their performance worsened, but it improved when given only one dose on the first day.

Conclusions: These results indicate that a strong activation of alpha5GABAARs can improve visual and social working memory, but a slight activation can improve long-term, particularly spatial memory. This can help in further analyzing the role of alpha5GABAARs in cognition, and potentially be used in treating cognitive impairments that accompany various disorders.

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EEG-BASED MEASURES VERSUS SOCIAL MEDIA ENGAGEMENT

Jelena Veinović Stevanović, Velimir Štavljanin, Jelena Jovanović
Faculty of Organizational Sciencies, University of Belgrade, Belgrade, Sebia

veaedea@gmail.com

Aims:Thisstudyaimedtodemonstrateempiricallythatconsumers'attentionisrelatedtochangesintheelectroencephalographic (EEG) brain activity during the observation of a viral and non-viral advertisement displayed on social media, as well as correlation of total number of social media engagement on posted content. Online environment makes concealing real thoughts easy. Hence, the skill of observing consumers' actual responses to advertising via brain activity has useful implications.

Using EEG as a tool we are able to get the right data behind users attention and brand recall. The study will be concentrated on two-part experiment: First will be the EEG gathering via EmotivEpoc 14 channel EEG device and questionnaire poll in order to cross check memory index and self-reflective memory on the viral video in regard of the brand recall.

The results are processed via signal filtering and statistical data processing. EEG and survey results will show correlation between social media metrics and neuroengagment.

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ALPHA ASYMMETRY INDEX OF PREFRONTAL AND TEMPORAL REGIONS PREDICTS TREATMENT RESPONSE TO REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

Stojadinović G[1], Yadollahpour A[2], Kesić S[1], Spasić S[3,4]

[1]Department of Neurophysiology, Institute for Biological Research"Siniša Stanković", University of Belgrade, Belgrade, Serbia.
[2]Department of Medical Physics, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
[3]Department of Life Sciences, Institute for Multidisciplinary Research, University of Belgrade, Belgrade, Serbia.
[4]Faculty of Informatics and Computing, Singidunum University, Belgrade, Serbia

ggrbic@ibiss.bg.ac.rs

Aims: The aim of this study was to investigate the value of alpha asymmetric index (AAI) in predicting treatment response in two different protocols of rTMS in patients with intractable major depression.

Methods: A single-blind clinical trial was conducted in patients with intractable major depression. Patients (n=34) were divided into two treatment groups underwent two different rTMS protocols (20Hz rTMS and 10Hz rTMS). Hamilton depression rating scale-17 items (HDRS-17) was used to divide the patients into responders and non-responders. The AAI in prefrontal (Fp1-Fp2), frontal (F3-F4, F7-F8), and temporal (T3-T4) regions were calculated and compared between pre- and post-intervention in each group and between the responders and non-responders.

Results: In the 20Hz rTMS group responders, 6 patients responded to the treatment, whereas 10Hz rTMS showed 8 responders. In the responders of 20 Hz rTMS, the AAI at Fp1-Fp2, F3-F4, and T3-T4 significantly decreased after the intervention ($P<0.05$). The responders of 10 Hz rTMS showed a significant reduction in the AAI at Fp1-Fp2 and T3-T4 regions after the intervention ($P< 0.05$). The AAI values for this group insignificantly decreased at F3-F4 and F7-F8 regions after the intervention. The non-responders in 10Hz rTMS did not show a significant change in the three regions. The two groups of responders did not show any significant difference in AAI in the four regions indicating the AAIs for both protocols could be a reliable marker for predicting treatment response.

Conclusions: It seems AAI at prefrontal and temporal regions could be used for prediction of treatment response, regardless of rTMS protocol.

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FRAILTY INDEX VS FRAILTY SCORE IN 5XFAD MOUSE MODEL OF ALZHEIMER'S DISEASE: THE INFLUENCE OF AGE AND GENDER

Todorovic S, Loncarevic–Vasiljkovic N, Jovic M, Sokanovic S, Kanazir S, Mladenovic Djordjevic A

Department of Neurobiology, Institute for Biological Research "Sinisa Stankovic", University of Belgrade, Belgrade, Serbia

smilja.pracer@ibiss.bg.ac.rs

Development of Alzheimer's disease (AD) is correlated with increased frailty, indicating that a "frail brain" might be more susceptible to neurological problems like dementia since it is less able to cope with the pathological burden. Defining frailty status represents a convenient approach for detecting individuals with increased vulnerability for developing more severe form of AD. Moreover, frailty assessment has a role as an important research tool for validating existing and potential AD therapeutics. One of the most widely used transgenic animal model in AD research is 5xFAD transgenic mouse, but frailty in this model is poorly investigated. We performed the first comprehensive investigation of frailty status in 5xFAD mice based on sex and age differences.

All measurements were performed on 3-month-old and 11-month-old 5xFAD transgenic male and female mice. For frailty measurements, two validated mouse frailty assessment tools were used: phenotypic frailty score (FS) and clinical frailty index (FI).

We observed prominent increase in frailty with age in both sexes, although females were notably less frail than males. Using FI approach, we detected significant difference between young and old males and females. On contrary, using FS approach we could not detect age related differences in 5xFAD females.

Comparison of frailty index and frailty score revealed a substantial difference in detected frailty status, with FI being identified as more sensitive approach in frailty assessment as opposed to FS. These results suggest precaution when choosing frailty tool and imposes the need for further adaptation of frailty measurements in mouse models of AD.

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AGE-RELATED COGNITIVE IMPAIRMENT IN DOGS

Zuzana Mojzisova[1], Filip Humenik[1], Jana Farbakova[2], Aladar Madari[2], Lydia Mesarcova[3], Lenka Skurkova[3], Barbara Petkova[3], Dasa Cizkova[1]

[1]Department of Anatomy, University of Veterinary Medicine and Pharmacy in Kosice, Kosice, Slovakia. [2]University Veterinary Hospital, UVMPH in Kosice, Kosice, Slovakia. [3]Department of Applied Ethology, UVMPH in Kosice, Kosice, Slovakia

moses.zuz@gmail.com

Aims: The aim of our study was to diagnose and stratify dogs with cognitive impairment and analyse neurodegenerative changes.

Methods: In our study we examined 10 dogs (>8 years) involving CADES (CAnine DEmentia Scale), Osella questionnaire and Open Field examination. All dogs were evaluated clinically and neurologically and those with systematic diseases were excluded from our study. The presence of β-amyloid plaques, neurofibrillary tangles and inflammation in two post-mortem brains (CCDS) was evaluated.

Results: We have identified six dogs with mild cognitive impairment by CADES, showing behavioural changes, such as disrupted owner-pet relationship, elevated vocalization and irritability. The senile plaques in brain tissue were exclusively in diffuse form as observed in normal aging human brain. Neuro-inflammation in examined dogs was represented by reactive and senescent microglia.

Conclusions: CADES with Open Field and complex clinical examination seems to be proper diagnostic approach to patients with CCDS. Senior dogs are suitable model for studying aging process and early AD pathology, but cannot be fully considered as an appropriate model to study whole complex of AD stages.

Supported: APVV15-0613, IGA UVLF 02/2019" Stratification of patients with canine cognitive dysfunction, application of innovative stem cell therapy".

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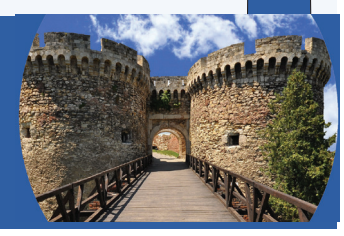

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BEHAVIORAL SIGNATURES OF SOCIAL INTERACTION AND BPSD-LIKE BEHAVIORS FOR BEHAVIORAL MONITORING OF 3XTG-AD MICE AND NTG MICE DURING HOUSING ROUTINES

Lydia Giménez-Llort [1,2], Virginia Torres-Lista [1,2], Aida Muntsant-Soria [1,2]

1Institut de Neurociències, Universitat Autònoma de Barcelona, Bellaterra, Spain. 2Department of Psychiatry and Forensic Medicine, Faculty of Medicine, Universitat Autònoma de Barcelona, Bellaterra, Spain

lidia.gimenez@uab.cat

Aims: Modeling Alzheimer's disease in rodents has been addressed using methodological approaches based on the interaction of the subject with the environment, but few involve the relation with other individuals. Social neuroscience efforts to fill this gap are also foreseen as important to improve the predictive validity of new preventive and/or therapeutic strategies. The present work is aimed to know if social interaction analysis can be also used as a non-intrusive method for behavioral monitoring of these models during husbandry routines.

Methods: Social interaction among dyads of two mice (same sex and genotype) introduced in a new home cage was depicted to identify behavioral signatures of dysfunction in 3xTg-AD mice at ages mimicking early- to advanced-stages of disease, and as compared to age- and sex-matched non-transgenic mice of the same genetic background with normal aging. Behaviors were classified and scored (episodes and duration) into social (social investigation, aggression, vibrant tail) and non-social (exploring, digging, self-grooming) interactions.

Results: Vibrating tail, digging, body/face social contact and self-grooming where the most sensitive variables to 3xTg-AD genotype. Besides, sex-specific signatures (vibrating tail, digging and self-grooming) characterized the female 3xTg-AD mice ethogram.

Conclusions: The identification of genotype and sex-specific variables of behavior that can be used as signatures are of special interest for behavioral monitoring in husbandry routines and in the follow-up monitoring prior to assessment of preventive/therapeutical strategies. The present results also contribute to the growing efforts to study social behaviors in rodents with special attention to their complexity in models of Alzheimer's disease.

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MECHANISMS OF MONOMERIC C REACTIVE PROTEIN INDUCING NEURODEGENERATION

García-Lara E[1,2], Aguirre S[1], Clotet N[1], Corpas R[1], Slevin M[2,3], Sanfeliu C[1]

1Institut d'Investigacions Biomèdiques de Barcelona, CSIC, IDIBAPS and CIBERESP, Barcelona, Spain;
2Targu Mures University of Medicine and Pharmacy, Targu Mures, Romania;
3Faculty of Science and Engineering, School of Healthcare Science, Manchester Metropolitan University, Manchester, United Kingdom.

elisaglara21@gmail.com

Aim: Neuroinflammation derived from ischemic damage increases the risk of both vascular dementia and Alzheimer's disease (AD). The monomeric C- reactive protein (mCRP) formed in the dissociation of the pentraxin CRP within the extracellular matrix of ischemic tissue, may be a causative link between stroke-associated inflammation and memory loss. We aimed to investigate the mechanism underlying neuroinflammation and loss of neuroplasticity induced by mCRP.

Methods: We used our established in vivo model of dementia by bilateral hippocampus injection of mCRP in C57BL/6j mice. Transgenic AD mice 5XFAD were used for comparison. Cell lines of microglia BV2 and HMC3 and neuroblastoma SH-SY5Y were treated with mCRP or CRP. Microglial cells were also treated with lipopolysaccharide. We assayed hippocampus tissue and cell culture extracts for gene expression and protein levels in a search of changes underlying neuroinflammation, neuroplasticity loss and neurodegeneration.

Results: In vivo treatment with mCRP induced long-term loss of learning and memory, analyzed up to 6 months. First molecular results revealed lower activation of signaling pathways related to plasticity early genes Arc and Egr1 in mCRP mice. Main changes in 5XFAD were related to oxidative stress and gliosis markers. A main effect on protein processing induced by mCRP was hyperphosphorylation of tau in AD-associated pathogenic residues such as Ser202 and Ser396. We are analyzing the protective effects of anti-inflammatory agents.

Conclusions: Characterizing the mechanisms of mCRP-induced dementia might contribute to fight against AD incidence in the elderly.

Funding: EU-COP 2014-2020, CRP-SAD, ID: P_37_674, MySMIS code: 103432, contract: 51/05.09.2016; SAF2016-77703, MINECO and ERDF; 2017-SGR-106, AGAUR.

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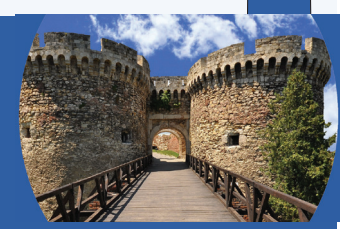

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DIFFERENTIAL IMPACT OF SPECIFIC MIDBRAIN TO STRIATAL CHOLINERGIC INTERNEURONS PATHWAYS ON ASSOCIATIVE LEARNING

Zhuoliang Li, Norbert Krebs, Giorgio Rizzi & Kelly R. Tan
Biozentrum, University of Basel, Basel, Switzerland

zhuoliang.li@unibas.ch; kelly.tan@unibas.ch

Aims: The rare tonically active striatal cholinergic (ChAT) interneurons, responsive to relevant environmental cues, are strongly implicated in reinforced learning. Past work on their upstream regulators focused on the cortex and thalamus, however, we believe other inputs might feed ChAT neurons with behaviorally relevant information. We suggest that midbrain neurons might be key in this process and hypothesized that specific midbrain (glutamatergic VGluT2-, GABAergic VGAT-, and dopaminergic DAT- expressing) subpopulations modulate ChAT neurons either directly or indirectly via the thalamus (parafasicular nucleus Pf) to influence fear learning.

Methods: To unravel the connectivity between the specific midbrain populations and striatal ChAT neurons, we take advantage of specific transgenic lines to investigate the anatomical circuity with viral tools and the functional connectivity with in-vitro electrophysiology. We then optogenetically silenced the direct and indirect glutamatergic and GABAergic pathways in discriminatory auditory fear conditioning. With single-cell calcium imaging in behaving animals, we study the activity of midbrain cells to relevant cues before, during, and following fear learning.

Results: We observe that midbrain glutamatergic and GABAergic but not dopaminergic neurons directly connect with striatal ChAT and Pf neurons. The silencing of these inputs during fear conditioning result in unique shifts in the discrimination of predictive cues. Furthermore, midbrain neurons exhibit diverse responses to these cues that can be modulated following learning.

Conclusions: We provide converging evidence on how specific midbrain subpopulations connect with striatal ChAT neurons and their behavioral significance. Moreover, we gain insights into how midbrain neurons respond and become entrained to predictive cues.

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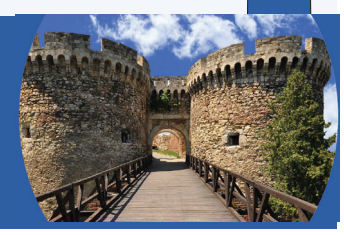

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ARE CALBINDIN AND PARVALBUMIN INTERNEURONS INCLUDED INTO THE SPINAL NETWORKS RESPONSIBLE FOR THE PATTERN FORMATION OF THE LOCOMOTION?

Veshchitskii A.[1], Merkulyeva N.[1,2,3], Musienko P.[1,2,3]

1Pavlov Institute of Physiology RAS, St. Petersburg, Russia;
2Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia;
3Russian Research Center of Radiology and Surgical Technologies, Ministry of Healthcare of the RF, St. Petersburg, Russia

veschickiyalex@mail.ru

The aim of this study was to identify the morpho-functional organization of the neuronal spinal networks controlling hindlimb locomotion and contributing to the pattern formation level of the central pattern generator, by mean of combination of the c-fos technique and immunohistochemical staining for the markers of the interneuronal populations.

Methods: (1) Epidural electrical stimulation of the lumbar spinal cord, evoking locomotion of the hindlimbs in cat; (2) Using an immediately early gene c-fos technique for the visualization of the spinal neurons activated during locomotion expression; (3) Immunohistochemical revealing of the spinal interneurons expressing calcium-binding proteins calbindin and parvalbumin, (4) Comparison of two patterns of the distribution of the interneurons immunopositive to c-fos, calbindin, and parvalbumin.

Results. C-fos-immunopositive neurons were located throughout the gray matter but mainly, in the medial (and, in a less extent, lateral) part of the intermediate gray matter (IGM). Calbindin-immunopositive neurons were located predominantly in the dorsal horns, but clear clusters were observed in the medial and lateral IGM. A maximal density of the parvalbumin-positive neurons was obtained in the medial region of the IGM, but more dorsally than calbindin-positive neurons did.

Conclusions. We suppose that the distribution of c-fos-positive neurons mirrors the pattern of the distribution of the spinal locomotor interneurons. Since two closely located interneuronal clusters expressing calbindin and parvalbumin respectively were found in the medial region of the IGM, we believe that this area can be a part of the integrative neuronal networks responsible for the pattern formation during locomotion.

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THE EFFECTS OF STRESS ON MOTIVATED BEHAVIOUR DEPEND ON TRAIT ANXIETY IN RATS

Ioannis Zalachoras, Simone Astori, Jocelyn Grosse, Isabelle Guillot-de Suduiraut, Olivia Zanoletti, Carmen Sandi
Laboratory of Behavioral Genetics, Brain Mind Institute, EPFL, Lausanne, Switzerland

ioannis.zalachoras@epfl.ch

Aims: Mesolimbic dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) play a critical role in motivated behaviour. Corticotropin releasing-hormone (CRH) acts on the VTA to modulate stress effects on motivated behaviour, however, whether these effects depend on individual differences in trait anxiety is unknown.

Methods: We measured VTA expression of CRH receptor 1 (CRHR1) in male outbred Wistar rats classified as low-anxious (LA) or high-anxious (HA), depending on their elevated plus maze performance. To investigate whether stress interacts with trait anxiety to modulate motivated behaviour, we tested the effects of acute stress on the progressive ratio paradigm. We downregulated CRHR1 expression in the VTA using antisense oligonucleotides. Finally, we measured dopamine release in the NAc and assessed dopaminergic neuron responses to CRH using microdialysis and patch-clamp recordings in VTA slices, respectively.

Results: LA rats had higher CRHR1 expression than HA rats in dopaminergic neurons. Stress or intra-VTA CRH infusion resulted in improved performance in LA, but impaired performance in HA rats. Antisense-mediated downregulation of CRHR1 in the VTA blocked stress effects in LA rats. Following intra-VTA CRH infusion, NAc dopamine release was higher in LA than HA rats. CRH application increased firing of dopaminergic neurons in LA rats to a larger extent than HA rats, which was abrogated after CRHR1 downregulation in the VTA.

Conclusions: Our findings indicate that stress effects in motivated behaviour depend on trait anxiety and may be mediated by differences in the CRHR1 modulation of the mesolimbic dopaminergic system.

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INVESTIGATION OF THE EFFECTS OF L-CARNITINE ON AGE-RELATED LEARNING CHANGES AND GLUTAMATE PATHWAY

Güven Akçay[1], Betül Danışman[1], Çiğdem Gökçek-Saraç[2], Mutay Aslan[3], Narin Derin[1]

[1]Akdeniz University, Faculty of Medicine, Department of Biophysics, Antalya, Turkey. [2]Akdeniz University, Faculty of Engineering, Department of Biomedical Engineering, Antalya, Turkey. [3]Akdeniz University, Faculty of Medicine, Department of Biochemistry, Antalya, Turkey

guvenakcay@akdeniz.edu.tr

Aims: As a physiological result of aging, impairments in communication between brain neurons and cognitive functions diminish, and also changes in the activity of glutamatergic cells and in glutamate transporters increase the sensitivity of neurons to glutamate toxicity. The aim of this study was to investigate the relationship between L-carnitine, a potent antioxidant and antioxidant effect, with glutamate cycle and receptors in the hippocampus.

Methods: 10-months-old male Wistar rats were divided into two groups(30 rats in each group): Control and LCAR. Learning experiment was conducted with the object recognition test. Levels of L-Carnitine, glutamate transporters(GLUT-1,2, EAAT-1,2,3), glutamate-glutamine concentration, the oxidant and antioxidant capacities in the hippocampus and brain were measured. The obtained data was analyzed by T-test and One-Way ANOVA.

Results: It has been found that LCAR levels in the brain and plasma were measured significantly higher than the C group. The L-Car group had higher learning and memory performance at the object recognition test compared to the C group($p \leq 0.05$). Compared to C group, glutamate transporters(VGLUT1, VGLUT2, EAAT1,2,3) increased only in hippocampus tissue in carnitine group, while glutamate and glutamine increased significantly in both hippocampus and brain tissues. When compared with the control group, while the oxidant capacity at the brain and hippocampus decreased due to the LCAR treatment, the LCAR treatment decreased the antioxidant capacity only at the hippocampus.

Conclusions: L-carnitine has positive effect on aging-associated cognitive disorders and this effect is related to the glutamate regulation in brain tissue(Project Number: TSA-2017-2884-Akdeniz University).

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INVESTIGATION OF ANTINOCICEPTIVE EFFECT OF CHRYSOPHTHALMUM MONTANUM (DC.) BOISS. EXTRACT IN MICE

Tansu Alan[1], Sultan Alan[2], Serpil Demirci Kayıran[3], Umay Merve Güven[4], Fazilet Aksu[5]

1Department of Biotechnology, Çukurova University, Turkey. 2Department of Midwifery, Faculty of Health Sciences, Çukurova University, Turkey 3Department of Pharmaceutical Botany, Faculty of Pharmacy, Çukurova University, Turkey. 4Department of Pharmaceutical Technology, Faculty of Pharmacy, Çukurova University, Turkey. 5Department of Medical Pharmacology, Çukurova University, Turkey

tansualan@gmail.com

Aims: Chrysophthalmum montanum (DC.) Boiss. (CM) is a naturally growing plant in Eastern Turkey. In Turkish folk medicine, the aerial parts of CM are used to treat common cold, sinusitis, artrits pains and for wounds. Its antiproliferative activity was studied, but other effects have not been examined yet. In this study we examined antinociceptive effect of CM extract in mice using hot-plate and tail-flick tests.

Methods: The aerial parts of CM were collected from the Dogansehir, Malatya, Turkey. The powdered plant material was macerated at room temperature in methanol:dichloromethane (MD,1:1,v/v) for 72 h and this process was repeated for 2 times. The extraction solvents combined by filtration and evaporated under reduced pressure at 40 0C to obtain the crude CM-MD extracts (19.48g). CM-MD extracts formulated as micro emulsion form for oral administration. Pseudo-ternary phase diagrams were constructed by using different oils and co-surfactants. The final formulation was prepared with isopropyl myristate, Span, Tween, ethanol and distilled water.CM-MD formulation and standard analgesic-antipyretic paracetamol was given to male mice by gavage (01.ml/10 g bw). The antinociceptive effects of drugs were determined by hot-plate and tail-flick tests.

Results:CM-MD formulation showed antinociceptive activity in the tail-flick test ($p<0.005$, t-test) while paracetamol did not. In the hot-plate test both drugs produced antinociceptive activity ($p<0.005$, t-test).

Conclusions: Results show that CM-MD formulation has an anticociceptive activity in hot-plate and tail-flick test in mice. Our results are noteworthy to develop advanced research for this plant.

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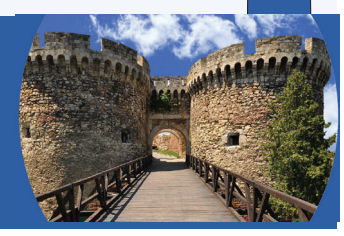

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THE EFFECTS OF AGMATINE ON DEPRESSION AND ANXIETY-LIKE BEHAVIOR IN MATERNAL SEPARATION MODEL IN RATS

Feyza Aricioglu[1], Hacer Zortul [1], Cangul Yutdas[1], Bayram Yilmaz[2]

1Marmara University, School of Pharmacy, Department of Pharmacology and Psychopharmacology Research Unit, Istanbul-Turkey. 2Yeditepe University, School of Medicine, Department of Physiology, Istanbul-Turkey

hacerzortul@gmail.com

Aims: Early-life stress is a risk factor for several psychiatric disorders. Maternal separation (MS) is a model, characterized by behavioral, neuroendocrine, neuroimmune and neurotrophic changes due to exposure to stress during neurodevelopmental stage. Agmatine is an endogenous molecule which has anti-stress, antidepressant-like and anti-inflammatory effects. Current study designed to examine possible antidepressant/anxiolytic capacity of agmatine in a neurodevelopmental model in rats.

Methods: Sprague-Dawley male rats were divided into groups as Control, MS, MS+Fluoxetine (10mg/kg, for 12days), MS+Agmatine (40mg/kg, for 12days). The MS procedure included separating the offspring from the mother for 20 days after birth followed by social isolation period untill postnatal day-23. Then behavioral tests such as forced swim (FST), elevated plus maze (EPM), open field (OFT), and body splash tests (BST) were performed. Data were analyzed by one-way analysis of variance (ANOVA), followed by post-hoc Tukey's multiple comparison tests. Differences with $p < 0.05$ were considered statistically significant.

Results: MS induced depressive-like state in the FST and grooming, anxiety-like behaviour in EPM and BST, hyperactivity-like symptoms in OFT. Both fluoxetine and agmatine treatments decreased these depressive and axiety-like symptoms in FST and EPM while only agmatine treatment significantly inhibited hyperactivity like symptoms.

Conclusions: MS is a neurodevelopmental model of depression which is highly related with adulthood hyperactivity-like symptoms. According to results of the current study agmatine have beneficial neuromodulatory effects on early-life stress related disorders. Further research is required to understand the molecular mechanisms beyond.

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EFFECTS OF TOPIRAMATE ON LEARNING AND MEMORY IN RATS EXPOSED TO CHRONIC UNPREDICTABLE MILD STRESS

Sule Aydin[1], Birce Ercelen[2], Zeynep Gul Sanli[1], Cansu Kilic[1], Fatma Sultan Kilic[1]

1Eskisehir Osmangazi University, Medical School, Department of Pharmacology. Eskişehir, Turkey. 2Eskisehir Osmangazi University, Medical School, Department of Anatomy. Eskişehir, Turkey

ssuleaydin@gmail.com

Aims: Chronic unpredictable mild stress (CUMS) is an important etiologic factor for neurodegenerative disorders characterized by amyloid-b accumulation, neuronal loss, learning-memory impairment. Topiramate(TPM), as an antiepileptic drug, has contradictory dose-dependent effects on cognitive functions in the literature. We aimed to investigate the advantages and drawbacks of high and low doses of TPM.

Methods: Wistar-male rats were used and divided into 7-groups; Control, CUMS, CUMS+TPM(0.1,1,10,100mg/kg/p.o.), Control+TPM(1mg/kg/p.o.). CUMS-groups were subjected to nine different-type of stressors for 45-days. After CUMS-protocol, drugs were administrated for 21-days. Anhedonic-behaviors were evaluated by sucrose-preference test. Spatial-learning/memory were evaluated by water-maze test and anxiety and depression were evaluated by plus-maze and forced-swim test. One/Two Way ANOVA tests were used for statistical analysis.

Results: In spatial-memory, escape-latency increased for the first 2-day testing and cumulative duration increased in CUMS compared to control in last day. Spatial-learning/memory impaired in CUMS+Top10/Top100-groups compared to control/CUMS-groups. Spatial-memory improved in CUMS+Top1/Top0.1-groups compared to control. In forced-swim, immobility-time increased in CUMS compared to control and CUMS+Top10/Top100-groups while CUMS+Top0.1 increased compared to control. The time spent in the open arms of the plus-maze were comparable in all-groups. In locomotor-activity, CUMS/CUMS+Top0.1 increased compared to control while CUMS+Top10 decreased compared to CUMS in total-activity. In the CUMS group , 62.5% of the rats showed a sucrose-preferece. Under %65 of sucrose-preference is defined as anhedonia.

Conclusions: Our results showed that CUMS improved memory and Top1/0.1mg/kg doses did not impaired this effect. Top100/10mg/kg doses have antidepresstant-like effect. After the experiments brain-derived-neurotrophic-factor(BDNF), neuron-diameter/volume, dendritic-extensions of rats will be evaluated in hippocampus/gyrus-dentate.

This study is a part of an ongoing project which is supported by the Commission of Scientific Researches Projects in Eskisehir Osmangazi University (Project number : 2017-1771)

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EFFECTS OF EXCESSIVE SUGAR CONSUMPTION ON VOLUMETRIC MEASUREMENTS OF THE AMYGDALA IN RATS EXPOSED TO POST-TRAUMATIC STRESS DISORDER-LIKE CONDITIONS

İlkim Büyükgüdük [1], Elif Polat Çorumlu[1], Birce Erçelen[2], Emel Ulupınar [1,2]

1Eskişehir Osmangazi University, Health Science Institute, Interdisciplinary Neuroscience Department, Eskisehir, Turkey. 2Eskişehir Osmangazi University, Faculty of Medicine, Department of Anatomy, Eskisehir, Turkey

buyuk.ilkim@gmail.com

Aims: Neural circuitry involved in fear and anxiety is highly conserved throughout evolution and might be activated by a number of stressors in animal models. In this study, we aim to investigate the effects of excessive sugar consumption on the amygdala morphology of animals exposed to post-traumatic stress disorder (PTSD)-like conditions.

Methods: Adult Sprague-Dawley female rats (n=14) were divided into two groups. One group received a diet supplemented with 10% corn syrup for 10 days whereas the second one is fed with standard pellets. At the end of the dietary regimen, single prolonged stress protocol, including 2-hour immobilization, followed by 20-minute forced swim and ether anesthesia, was applied both groups. One week later, a reminder was applied by exposing animals to excessive light and sound conditions to produce PTSD-like symptoms. Animals were sacrificed to process for morphometric analysis, after testing their social recognition behavior. Amygdala volume was calculated by using Cavalier's volume estimation method on sections stained by toluidine-blue.

Results: Animals displayed comparable deterioration in their social behavior since the sniffing number of novel and familiar rats were similar in both groups. However, no significant difference was observed in volumetric measurements of the amygdala between animals exposed to PTSD-like conditions (1.07±0.05) and those also receiving excessive sugar consumption (1.19±0.12).

Conclusion: In animals exposed to PTSD-like conditions, social recognition behavior is negatively affected regardless of the excessive sugar consumption. Although PTSD-like conditions has an adverse effect on the social behavior, it is inefficient to produce alterations at volumetric level.

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EFFECTS OF CHLOROGENIC ACID ON CISPLATIN INDUCED PERIPHERAL NEUROPATHY AND NEUROTOXICITY

Cigdem Cengelli Unel, Ezgi Bozkurt, Kevser Erol

Eskisehir Osmangazi University, Faculty of Medicine, Department of Pharmacology, Eskisehir, Turkey

cigdemcengelli@gmail.com

Aim: Cisplatin(CIS) is an anticancer agent that is commonly used for several cancers. Peripheral neuropathy is a serious problem in CIS use. Chlorogenic acid(CA) is a dietary phenolic compound that is reported for its antioxidant, anti-inflammatory, neuroprotective, cytoprotective effects. CA was shown to have analgesic activity in different neuropathic pain models. The study aimed to investigate the acute and chronic effects of chlorogenic acid in CIS-induced peripheral neuropathy and neurotoxicity in vitro.

Methods: CIS 3 mg/kg was applied male Sprague Dawley rats (250-350kg, n=8) once a week for five weeks. Neuropathy was tested by using mechanical alloydnia. In acute, CA (50, 100 or 200 mg/kg) was used after 35 days. The neuropathy was tested 1 hour and 3 hours after the injection time. In chronic, CA was concurrently applied with CIS. The difference between day 0 (basal) and day 35 was evaluated. CA (10-1000 µM) was applied with submaximal concentration of CIS (200µM) to primary dorsal root ganglia. MTT assay was used to detect neurotoxicity. The data was analyzed by using SPSS 15. $p<0.05$ was accepted as significant.

Results: Mechanical allodynia was induced by CIS after 35th day. In acute, all doses of CA significantly increased paw withdrawal latency in mechanical allodynia test especially 1h after the CA injection. When CA was applied concurrently with CIS, the impaired withdrawal latency was also improved. Higher concentrations of CA seem to protect dorsal root ganglion cells against CIS toxicity.

Discussion: Consequently CA seems to have beneficial effects against neuropathic and neurotoxic effects of cisplatin.

This study was supported by "Scientific Research Projects" of Eskisehir Osmangazi University (Project No: 2016-1384)

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EFFECTS OF PIRACETAM ON THE DEVELOPMENT OF MORPHINE-INDUCED ANTINOCICEPTIVE TOLERANCE AND DEPENDENCE IN MICE

Seckin Engin[1], Elif Nur Barut[1], Yesim Kaya Yasar[1,2], Mine Duman[3], F. Sena Sezen[1,2]

1Department of Pharmacology, Faculty of Pharmacy. 2Drug and Pharmaceutical Technology Application and Research Center. 3Department of Medical Pharmacology, Faculty of Medicine, Karadeniz Technical University Trabzon, Turkey

seckinengin@ktu.edu.tr

Aims: Antinociceptive tolerance (AT) and dependence are major challenges of long-term opioid use in pain management. Although the exact mechanism and prevention of opioid tolerans is not known, several studies suggest an association of adaptive changes in neurotransmitter systems and oxidative stress. Piracetam (PM), a nootropic drug used for various indications including cognitive disorders and stroke, has been suggested to interact with neuronal transmission and oxidative stress. This study investigated the effect of PM on the development of morphine-induced AT and physical dependence in mice.

Methods: Male Balb/c mice (30-35 g, n= 8-12/group) were treated with morphine (10 mg/kg, s.c.) or saline (control) twice daily for 5 consecutive days (induction period) to induce AT. During induction period, mice received PM or saline twice (100, 250 and 500 mg/kg; i.p.) 30 min before morphine administration. On day 6, nociception was evaluted by using hot plate test (latency) and physical dependence was evaluated by naloxone (5 mg/kg; i.p.)-precipitated withdrawal signs (jumps and body weight loss).

Results: Repeated morphine administration resulted in the development of AT and dependence in mice demonstrated by significantly decreased latency time and withdrawal signs ($p<0,05$). Co-administration of PM at 250 mg/kg dose significantly attenuated AT ($p<0.05$) whereas naloxone-precipitated withdrawal remained similar with PM treatment ($p>0.05$).

Conclusions: Prevention of morphine tolerance without affecting the dependence in mice with PM co-administration indicates a new therapeutic potential in opioid tolerance. Further biochemical and molecular studies will clarify the underlying mechanism of this process.

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THE EFFECTS OF H2S ON THE ANTINOCICEPTIVE ACTIVITY OF DIPYRONE IN RATS

Kevser Erol, Çiğdem ÇEngelli Ünel, Mahsum Ayaz, Enes Yeşiltuna, Ezgi Demir, Hamza Dalçinar, Bengihan Özcan
Eskisehir Osmangazi University, Faculty of Medicine, Department of Pharmacology, Eskisehir, Turkey

kerol@ogu.edu.tr

Aim: Dipyrone is an analgesic, antipyretic and antiinflammatory drug that has been used for treating postopertive, colic, cancer pain, and migraine. It has some adverse effects such as of bone morrow suppression, sodium and water retention, and gastroenteropathy. H2S is a active-radical gas. The precursors of H2S were reported to overcome some drug side-effects. H2S was also shown to have activity against several pain-related situations. Study aimed to evaluate the contribution of H2S on central and peripheral antinociceptive activity of dipyrone.

Methods: Male six weeks old Sprague Dawley rats were divided into five groups (n=6): Control (Saline, ip); dipyrone (50 or 100 mg/kg i.p); NaHS (5mg/kg i.p); NaHS (5mg/kg) + dipyrone (50 mg/kg). Tail clip and hot plate tests were applied to the animals 30 minutes before and one hour after the drug injections. Five minutes after the injection of 60 mg/kg acetic acid (%0,6), stretching number was counted for ten minutes. The results were expressed as mean±SEM of latency, %MPE (maximal possible effect) and stretching number. One way and two way ANOVA tests were used for statistical analysis. $P<0.05$ was accepted as significant.

Results: Both doses of dipyrone did not have a significant activity on tail clip test, but 100 mg/kg dipyrone showed significant antinociceptive activity on hot plate and stretching tests. NaHS (5 mg/kg) was increased latency only on hot plate test. But the combination of NaHS with dipyrone has significant antinociceptive activity.

Conclusion: It seems that H2S increased the antinociceptive activity of diipyrone both central and peripherally.

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RESTING STATE EEG POWER DIFFERS DEPENDING ON AGE OF ONSET IN ALZHEIMER'S DISEASE

Ezgi Fide[1], Yağmur Özbek[1], İlayda Kıyı[1], Görsev G. Yener[2]

1Department of Neurosciences, Institute of Health Sciences, Dokuz Eylül University, Izmir, Turkey. 2Department of Neurology, Dokuz Eylül University Medical School, Izmir, Turkey

ezgifide@gmail.com

Aims: This study aims to investigate electrophysiological profile for individuals with early-onset Alzheimer's disease (EOAD), late-onset Alzheimer's disease (LOAD) in comparison with healthy controls (HC).

Methods: This study included 39 EOAD (19 CSF-proven), 31 LOAD (4 CSF-proven) patients and demographically-matched 36 young and 28 elderly controls. There was no difference between the MMSE scores of patient groups. Spectral-power analysis using Fast-Fourier Transformation (FFT) is performed on resting-state EEG data. Power in delta (0.5–3.9Hz), theta (4–7.8Hz), alpha-1 (8–10.2Hz), alpha-2 (10.6–12.2Hz), beta-1 (12.6–20Hz), and beta-2 (20.2–30Hz) frequency bands on frontal, central, parietal and occipital locations were compared among groups.

Results: There was a main GROUP effect on delta [$F_{3,130}=4.669$;$p=.004$] and theta [$F_{3,130}=10.139$;$p<.001$] power; indicating higher power in EOAD compared to young HC (all,$p<.024$) and LOAD (all,$p<.038$). There was a GROUPxLOCATION interaction effect [$F_{9,390}=7.806$;$p<.001$]; showing individuals with EOAD had higher theta power than young-HC in all locations, and LOAD in frontal and central locations. A main GROUP effect was found on alpha [$F_{3,130}=5.879$;$p=.001$], alpha-1 [$F_{3,130}=6.355$;$p<.001$] and alpha-2 [$F_{1,130}=6.195$;$p=.001$] power; indicating lower alpha and alpha-1 power in EOAD than young HC (all,$p<.011$). Young HC had higher alpha-2 power than elderly HC ($p=.009$). There was a main GROUP effect on beta-2 power [$F_{3,129}=3.75$;$p=.013$]; indicating lower power in EOAD than young HC ($p=.042$).

Conclusions: Different electrophysiological profiles observed in EOAD and LOAD. The changes in the electrophysiological dynamics are more common and widespread in EOAD compared to LOAD which may be related to the involvement of different brain regions.

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THE EFFECT OF SYMPATHETIC ANTAGONISTS ON THE ANTIDEPRESSANT-LIKE EFFECT OF DIPYRONE

M Kürşad Güçlü, Fatih Berktaş, Emine Ekemen, Olcay Kıroğlu, Fazilet Aksu
Department of Medical Pharmacology, Çukurova University, Turkey

kguclu0281@hotmail.com

Aims: In this study, the effect of sympathetic receptor antagonists on dipyrone–induced antidepressant-like action was studied using a mouse model of forced swimming test (FST).

Methods: FST was utilized to measure depression-like effects of dipyrone in male mice. In the FST, mice first tried to escape after they were placed in a container filled with water, but eventually exhibited immobility which was interpreted as antidepressant-like effect. Mice were divided to control, dipyrone (300 mg/kg), desipramine (300 mg/kg, tricyclic antidepressan), propranolol (2 mg/kg, non-selective β adrenergic receptor blocker), phenoxybenzamine (2 mg/kg, non-selective α adrenergic receptor blocker), prazosine (62.5 µg /kg, α1 adrenergic receptor blocker), and yohimbine (5 mg/kg, α2 adrenerjik receptor blocker) groups. Additional four groups that contained all blockers combined with dipyrone were also created. FST was performed 1 hour after intraperiteonal administration of all drugs. Results were analyzed using one way ANOVA followed by the Bonferonni post hoc test. This study is supported by Çukurova University Research Foundation (TSA-2018-11151).

Results: Immobility time decreased significantly in dipyrone, desipramine, propranolol, phenoxybenzamine and prazosine groups but not yohimbine group when compared with the control group. Dipyrone+phenoxybenzamine and dipyrone+yohimbine reduced immobility time also. No change was determined in dipyrone+prazosine and dipyrone+propranolol groups when compared with the control group.

Conclusions: Results show that dipyrone seems like to possess potential antidepressant-like effect and adrenergic receptors may play a role in this effect. Altough exact underlying mechanism can not be clarified with these results we can say that it depends on interactions with adrenergic system.

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SECOND BY SECOND RE-UPTAKE TIME CHANGINGS OF GLUTAMATE ON DEPRESSION INDUCED RATS

Ahmet Hacimuftuoglu[1], Kemal Alp Nalcı[1], Muhammed Sait Ertuğrul[1], İsmail Çağrı Aydın[1], Yeşim Yeni[1], Fatma Yeşilyurt[1], Bilal Nişancı[2], Nurullah Saraçoğlu[2], Bülent Çavuşoğlu[3], Damla Binnetoğlu[4], Ufuk Okkay[1]

1Ataturk University, Faculty of Medicine, Department of Pharmacology, Erzurum, Turkiye. 2Ataturk University, Faculty of Science, Department of Chemistry, Erzurum, Turkiye. 3Atatürk University, Faculty of Engineering, Electrical and Electronic Engineering, Department of Communication, Erzurum, Turkiye. 4Kafkas University, Faculty of Medicine, Department of Medical Pharmacology, Kars, Turkiye

hacimuftuoglu@gmail.com

Aims: Glutamate is the most common excitatory amino acide neurotransmitter in the brain and can cause neurodegeneration by excitotoxicity. Therefore, antagonism of glutamate receptors or the use of glutamate transporter activators is thought to reduce this excitotoxicity. We aimed to exhibit the relationship between depression and glutamate reuptake changings.

Methods: By chronic unpredicted stress model, applying various stressors to experimental animals for 40 days, depression had been occured. On the 20th day of stressor application, the treatment of ceftriaxone were started. Experimental animals were seperated into control, depression, and ceftriaxone groups. At the end of the experiment, behavioral tests were done, and glutamate re-uptake time on M1 (primary motor cortex) region of brain which is related with depression was measured via in vivo voltammetry technique. To better understand the role of glutamate in depression, we used an enzyme-based microelectrodes that were selective for glutamate and measures with fast temporal (2 Hz) and high spatial (15 × 333 µm) resolution.

Results: The total distance traveled indicated a meaningful difference interms of control group. (Total distance mean ± SD was 1420 ± 170 cm for control group and 1214 ± 244 cm for depression group) In in-vivo voltammetric study, a decrease in glutamate re-uptake time was also observed in depression group.

Conclusions: Ceftriaxon reversed the behavioural changes which were seen in depressed animals. Given treatments in M1 region recovered the decrease of glutamate reuptake time.

This study is supported by Ataturk University Project number: TOA-2018-6372

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RESTING-STATE DELTA POWER DIFFERENTIATES ALZHEIMER'S DISEASE FROM MILD COGNITIVE IMPAIRMENT AND HEALTHY AGED CONTROLS

Duygu Hünerli[1], Özgecan Kaya[1], Deniz Yerlikaya[1], Arzu Maharramova[2], Görsev G. Yener[2]

1Department of Neurosciences, Institute of Health Sciences, Dokuz Eylul University, Izmir, Turkey. 2Department of Neurology, Dokuz Eylul University Medical School, Izmir, Turkey

dhunerli@gmail.com

Aims: In this study, resting state EEG in Alzheimer's disease (AD) and amnestic mild cognitive impairment (aMCI) were investigated.

Methods: Twenty aMCI patients, 20 AD patients and 20 demographically-matched healthy controls (HC) were participated. EEG data was recorded for 4 minutes of eyes-closed condition according to the international 10-20 system. EEG rhythms of interest were delta (0.5-3.9 Hz), theta (4–7.8 Hz), alpha1 (8–10.4 Hz), alpha2 (10.5–13 Hz), beta1 (13–20 Hz), and beta2 (20–30 Hz). Sensitivity and specificity values were assessed using ROC analysis to distinguish AD from aMCI and HC.

Results: Repeated measures of ANOVA revealed main Group effects on delta [$F(2,57) = 8.353$; $p=0.001$], theta [$F(2,57)=5.038$; $p= 0.010$], alpha [$F(2,57) =3.837$; $p=0.027$], and alpha1 [$F(2,57)=4.209$; $p=0.020$] power between groups. Interaction effects of Anterior-Posterior Electrode Location x Group on delta [$F(6,171) = 2.621$; $p=0,038$], and theta [$F(6,171)=3.537$; $p=0.020$] power were observed, indicating compared with HC and aMCI group, patients with AD was characterized by increased delta and theta power in frontal, central and parietal electrode locations (for all; $p<0.040$). AD patients also showed decreased alpha and alpha1 power compared to HC (for all; $p<0.026$). Moreover, when using the cut-off score of >1.71 to identify AD from aMCI on central electrodes, and >1.73 to identify AD from HC on parietal electrodes yielded a sensitivity of 80.0% and a specificity of 80.0% for each.

Conclusion: Our findings indicate importance of delta EEG power as a neurophysiological marker in distinguishing AD from aMCI and from HC.

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ANTI-AGING EFFECT OF 7,8 DHF APPLICATION ON SENSORY MOTOR PERFORMANCE

Hatice Keser, Selcen Aydın Abidin, İsmail Abidin

Karadeniz Technical University, Faculty of Medicine, Department of Biophysics, Trabzon, Turkey

hatice.k35@gmail.com

Aim: Brain-Derived Neurotrophic Factor (BDNF) /Tropomyosin receptor kinase B (TrkB) signal pathway has a major role in neuronal survival and synaptic function. 7,8-Dihydroxyflavone(DHF) can mimic BDNF and activate BDNF/TrkB signal pathway. It can pass through blood brain barrier and is shown to rescue some hippocampal functions in some disease models. However, it isn't known how DHF affects cortical functions in aging. The aim of this study is to determine by behavioral tests how sensory motor functions alter with age, and how chronic DHF application affects them.

Methods: Male C57BL/6 mice were divided into three groups as young (5 months old), old (18 months old), old+DHF (18 months old). 5 mg/kg 7,8 DHF was administered to the old+DHF group and 17% DMSO was administered to young and old groups intraperitoneally for 3 weeks. At the end of administration three different behavioral tests were performed to test cortical sensory-motor functions. 1. Cylender test, 2. Hang wire test, 3. Adhesive removal test. Scoring and analysis were confirmed by the offline evaluation of video recordings. Statistical analysis were made by Kruskal-Wallis test.

Results: Old group were found to have lower performance than young and old+DHF groups in all behavior tests. This decrease was found to be statistically significant in hang wire ($p < 0.05$), and in adhesive removal tests ($p < 0.05$).

Conclusion: The findings revealed that 7,8 DHF administration exhibits anti-aging effects on motor cortex region depends on TrkB activation and may reduce cognitive disorders associated with aging.

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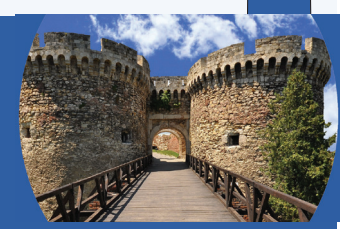

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ANXIETY AND PREPULSE INHIBITION LEVELS OF ADULT RATS EXPOSED TO DIVERSE REARING CONDITIONS

Fatma Sultan Kilic, Sule Aydin, Elif Polat Corumlu, Birce Ercelen, Bilgin Kaygisiz, Emel Ulupinar

Eskisehir Osmangazi University, Medical School, Department of Pharmacology, Eskisehir/ Turkey. Eskisehir Osmangazi University, Medical School, Interdisciplinary Neuroscience Department, Eskisehir/ Turkey. Eskisehir Osmangazi University, Medical School, Department of Anatomy, Eskisehir/ Turkey

fskilic@ogu.edu.tr

Aims: Prepulse inhibition (PPI) has been generally recognized as a simple operational measure of sensorimotor gating. Rearing conditions during prenatal and postnatal periods diversely affect development of the brain. We aimed to investigate behavioral responses to disruptive stimuli and anxiety level of animals exposed to prenatal stress (PS), maternal separation (MS), environmental-enrichment (EE).

Methods: In PS group (n:10), pregnant Sprague-Dawley rats were exposed to unpredictable stress paradigm between E14-E21. In MS group (n:12), offspring was separated from their dams and littermates for 3 hours between P2-P21. In PS-MS group (n:9) were exposed both PS and MS protocols. Animals raised in EE (n:8) were exposed to socially and physically complex environment until adulthood. Then, elevated plus-maze (EPM) and PPI tests were used to evaluate tendency of rats to anxiety and schizophrenia. One-way ANOVA test was used for statistical analysis.

Results: The time spent in the open arms of the EPM were comparable in all groups. There was a significant increase for only 74dB and 78dB prepulse intensities for EE group. Average PPI of PS-MS group significantly decreased compared to EE group.

Conclusions: Our results showed that raising animals in diverse environmental conditions alters their alertness to acoustics stimuli. In EE group, the significant effect for only lower prepulse intensities show the sensitivity increase. Since PPI reflects the fast, early-stage gating processing, heightening of PPI in animals raised in EE might reflect enhancement in higher-order cognitive and deeper central processing of the prepulse stimulus.

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P407

THE EFFECT OF DIPYRONE ON CYTOKINE LEVELS THAT INCREASED DURING CHRONIC STRESS

Olcay Kıroğlu[1], Fatih Berktaş[1], Erkan Maytalman[2], Fazilet Aksu[1]

1Department of Medical Pharmacology, Çukurova University, Turkey. 2Department of Medical Pharmacology, Alanya Alaaddin Keykubat University, Turkey

okiroglu2012@gmail.com

Aims: In this study, we aimed to investigate the role of cytokines in the antidepressant-like effect of dipyrone in chronic unpredictable mild stress model (CUMS).

Methods: Male mice were divided into control, stress and stress+dipyrone groups. CUMS model was used to induce depression. Mice were subjected to a variety of mild stressors several times a day for 6 weeks. Dipyrone (8 mg/g,ip) was administered to CUMS-exposed mice, each day beginning from the 2nd week. Splash, rota-rod (RR) and forced swimming (FST) tests were performed at the 7th week as behavioural tests. Coat state score (CSS) and weight of animals were recorded. Lastly, blood samples taken from mice were examined in proinflammatory IL1ß, IL6, IL17, IFN and TNF-α, antiinflammatory IL-10, GM-CSF, G-CSF levels. Results were analyzed using one way ANOVA followed by the Bonferonni post hoc test. This study is supported by Çukurova University Research Foundation (TSA-2016-5856).

Results:. Significant physical changes were observed in CSS. RR latency decreased and immobility time enhanced in FST test. The number of grooming decreased in the splash test. Dipyrone reversed the latency time and immobility time to normal values and augmented the number of grooming. The levels of proinflammatory cytokines were increased while antiinflammatory cytokine levels were unchanged in stressed mice. Proinflammatory cytokynes levels decreased to normal value while anti-inflammatory cytokines levels remained same in dipyrone applied group.

Conclusions: Results show that dipyrone has an antidepressant-like effect by decreasing proinflammatory cytokines levels which increase with stress on CUMS.

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P408

LOWER N1 WITH PRESERVED P1 VISUAL EVOKED RESPONSES IN CSF-PROVEN EARLY-ONSET MILD ALZHEIMER'S DISEASE

İlayda Kıyı[1], Deniz Atılgan[2], Ezgi Fide[1], Deniz Yerlikaya[1], Yağmur Özbek[1], Görsev G. Yener[2]

1Department of Neurosciences, Institute of Health Sciences, Dokuz Eylül University, Izmir, Turkey. 2Department of Neurology, Dokuz Eylül University Medical School, Izmir, Turkey

ilaydaky@gmail.com

Aims: In this study, we investigated differences in P1 and N1 evoked potential (EP) components between individuals with CSF-proven early-onset mild Alzheimer's Disease (EOAD) and healthy controls (HC).

Methods: Seventeen CSF-proven EOAD and 17 demographically-matched HC included in the current study. All participants underwent a comprehensive neuropsychological test battery. Light with 10 cd/cm2 luminance was used as stimulus. Peak amplitudes and latencies of P1 (90-150 ms) and N1 (130-200 ms) in frontal, central, parietal and occipital locations (3 channel for each location) were compared among groups. Statistical analyses were performed by repeated measures ANOVAs.

Results: There was no group differences P1 amplitude, P1 and N1 latency. There was a main group effect on N1 amplitude [$F(1,32)=9.642$ $p=0.009$]. Individuals with EOAD had lower N1 amplitudes compared to HC ($p=0.004$). There was a GROUPxLOCATION interaction effect [$F(3,96)=7.939$ $p=0.002$] with post-hoc tests revealing that individuals with EOAD had lower N1 amplitudes in comparison to HC on frontal, central and parietal locations (all, $p<0.007$). Location-wise, HC group had the highest N1 amplitudes over centrals with gradually decreasing toward parietal and occipital locations ($p<0.01$), whereas no such location difference was observed in EOAD.

Conclusion: Lower N1 amplitudes of EOAD might be related to the fact that N1 generators are located at cortical areas affected at earlier stages of EOAD. On the other hand, P1 generators that are located in primary visual cortex might not be involved yet. Further studies with different task demands or with volumetric MRI may shed a light on this subject.

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P409

ANALYSIS OF SELECTIVE ATTENTION TASK AND RESTING STATE EEG SIGNALS IN OBSTRUCTIVE SLEEP APNEA PATIENTS

Farhad Nassehi[1], Galip Özdemir[1], Nart Bedin Atalay[2], Melike Yüceege[3], Hikmet Fırat[3], Osman Eroğul[1]

1Department of Biomedical Engineering, TOBB University of Economics and Technology, Ankara. 2Department of Psychology, TOBB University of Economics and Technology, Ankara. 3Department of Chest Diseases and Sleep Center, Dışkapı Yıldırım Beyazıt Educational and Research Hospital, Ankara, Turkey

fnassehi@etu.edu.tr

Aims : Obstructive sleep apnea (OSA) is the most common respiratory sleep disorder. In this study EEG signals are recorded during both resting state and selective attention tasks. Aim of this study is investigating the variation of EEG signals in terms of Apnea Hypopnea Index (AHI) and Epworth's score during both tasks.

Methods : 10 voluntary OSA patients contributed to this study. Following their wake up, to measure their mental fatigue and attentional control level, volunteers participated in 3 minutes eyes-closed resting state and 13 minutes Simon-Flanker tasks respectively. During both tasks EEG signals are recorded from Fp, F, P, C and O places in both hemisphere according to the 10-20 electrode placement system. Spikes in EEG are removed by median filter and the remaining signal is splitted into 5 subbands (Delta, Theta, Alpha, Beta, Gamma). Relative power, absolute power, cordance value of each subband and (Alpha+Theta)/Beta, Theta/Alpha ratios of each channel are analyzed. Parameter variations are investigated in electrodes, sessions (Task, Resting state), lateralization (left, right) variables and their interactions among different groups. Mixed-ANOVA statistical method is implemented for analysis.

Results : Patients are divided into different groups (AHI>15 and Epworth>11). Meaningful differences are noted ($p < 0.05$) in electrodes and electrodes x lateralization interaction for all features, except that relative power of Gamma, Alpha bands and cordance value of Gamma band. All variables and interactions indicate meaningful differences ($p < 0.05$) in relative power of Beta band. Significant meaningful difference is also noted in electrode x lateralization x AHI>15 interaction in relative power of Delta band.

Conclusion : Parameters for Alpha and Theta bands, show negative relationship between two bands. This result coincides with previous findings in literature conducted on control groups.

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RESTING STATE EEG POWER DIFFERS DEPENDING ON AGE OF ONSET IN ALZHEIMER'S DISEASE

Yağmur Özbek[1], Ezgi Fide[1], İlayda Kıyı[1], Görsev G. Yener[2]

1Department of Neurosciences, Institute of Health Sciences, Dokuz Eylül University, Izmir, Turkey. 2Department of Neurology, Dokuz Eylül University Medical School, Izmir, Turkey

ozbekyagmur1@gmail.com

Aims: This study aims to investigate electrophysiological profile for individuals with early-onset Alzheimer's disease (EOAD), late-onset Alzheimer's disease (LOAD) in comparison with healthy controls (HC).

Methods: This study included 39 EOAD (19 CSF-proven), 31 LOAD (4 CSF-proven) patients and demographically-matched 36 young and 28 elderly controls. There was no difference between the MMSE scores of patient groups. Spectral-power analysis using Fast-Fourier Transformation (FFT) is performed on resting-state EEG data. Power in delta (0.5–3.9Hz), theta (4–7.8Hz), alpha-1 (8–10.2Hz), alpha-2 (10.6–12.2Hz), beta-1 (12.6–20Hz), and beta-2 (20.2–30Hz) frequency bands on frontal, central, parietal and occipital locations were compared among groups.

Results: There was a main GROUP effect on delta [$F_{3,130}=4.669$;$p=.004$] and theta [$F_{3,130}=10.139$;$p<.001$] power; indicating higher power in EOAD compared to young HC (all,$p<.024$) and LOAD (all,$p<.038$). There was a GROUPxLOCATION interaction effect [$F_{9,390}=7.806$;$p<.001$]; showing individuals with EOAD had higher theta power than young-HC in all locations, and LOAD in frontal and central locations. A main GROUP effect was found on alpha [$F_{3,130}=5.879$;$p=.001$], alpha-1 [$F_{3,130}=6.355$;$p<.001$] and alpha-2 [$F_{1,130}=6.195$;$p=.001$] power; indicating lower alpha and alpha-1 power in EOAD than young HC (all,$p<.011$). Young HC had higher alpha-2 power than elderly HC ($p=.009$). There was a main GROUP effect on beta-2 power [$F_{3,129}=3.75$;$p=.013$]; indicating lower power in EOAD than young HC ($p=.042$).

Conclusions: Different electrophysiological profiles observed in EOAD and LOAD. The changes in the electrophysiological dynamics are more common and widespread in EOAD compared to LOAD which may be related to the involvement of different brain regions.

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USAGE OF NOVEL OBJECT RECOGNITION TEST IN STRESSED ANIMALS TREATED WITH A SINGLE SUBANESTHETIC DOSE OF KETAMINE

Elif Polat Corumlu[1], Osman Ozcan Aydin[1], Ufuk Corumlu[2], Emel Ulupinar[1,2]

1Eskişehir Osmangazi University, Institute of Health Sciences, Department of Interdisciplinary Neuroscience, Eskisehir, Turkey. 2Eskişehir Osmangazi University, Faculty of Medicine, Department of Anatomy, Eskisehir, Turkey

epolatcorumlu@gmail.com

Aims: Natural propensity to the novelty of animals can be evaluated in a relatively short time, without an external motivation by the novel object recognition test (NOR). In this preliminary study, we wanted to investigate discrimination and recognition indexes of NOR to evaluate the cognitive capabilities of stressed animals following single subanesthetic dose of NMDA receptor antagonist ketamine injection.

Methods: Wistar male rats (n=8) were exposed to stress paradigm for 28 days, then treated with intraperitoneal saline or ketamine (10mg/kg) injections. Control animals (n=8) received similar treatments. In NOR test, animals were placed in an empty open field apparatus for 15 minutes. Next day, two identical rectangular objects were introduced for 5 minutes during the training session. In the test session, one of the objects was replaced by a spherical object. Discrimination index [DI = (TN– TF)/(TN+TF)] was calculated using the difference in exploration time for novel (TN) and familiar (TF) objects divided by total exploration time of objects (TN+TF). The ratio of TN by (TN+TF) was calculated as the recognition index [RI = TN/(TN + TF)].

Results:While the stress paradigm has no significant effects on DI and RI of animals; ketamine injection [(0,32±0,3),(0,53±0,2)] caused substantial decrease in these indexes comparing to both saline administered control [(0,39±0,1),(0,7±0,06)] and stress [(0,40±0,3),(0,53±0,2)] groups.

Conclusion: Our results implied that in stressed animals, ketamine administration impairs the recognition and retention processes of the memory. Future studies are necessary to reveal the influence of ketamine treatment on the hippocampus-dependent learning mechanisms and memory consolidation.

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ANTIDEPRESSANT AND ANXIOLYTIC EFFECTS OF PREGABALIN IN RATS AND COMPARISON WITH REFERENCE ANTIDEPRESSANT AND ANXIOLYTIC DRUGS

Zeynep Gul Sanli[1], Mustafa Erhan Civgin[1], Sule Aydin[1], Cansu Kilic [1], Setenay Oner[2], Cafer Yildirim[1], Fatma Sultan Kilic[1]

1Eskisehir Osmangazi University, Medical School, Department of Pharmacology, Eskişehir/ Turkey. 2Eskisehir Osmangazi University, Medical School, Department of Biostatistic, Eskisehir/ Turkey

zeynepgul_sanli@hotmail.com

Aim: Pregabalin is an orally used drug preferred in the treatment of treatment-resistant epilepsy, neuropathic pain, fibromyalgia and generalised anxiety disorder. It is structurally similar to gabapentin. However, its mechanism of action is not through GABA'ergic processes. We aimed to investigate the antidepressant and anxiolytic effects of pregabalin and comparing with other drugs.

Methods: Male Wistar Albino rats were used in the study and were divided 13-groups(n:7): control, pregabalin(5,10,20,40mg/kg), amitriptyline(10mg/kg), fluoxetine(5mg/kg), ketamine(10mg/kg), diazepam(5mg/kg) were administered intraperitoneally. Pregabalin(20mg/kg) was used in the combination groups. Elevated plus maze, locomotor activity and forced swimming tests were performed. Elevated plus maze test and forced swimming test were performed consecutively in this order. Results were statistically analysed with Kruskal-Wallis test and expressed as median and 25%-75% percentiles.

Results: Pregabalin indicated dose dependent anxiolytic effect and independend depressant effect in all doses. In the combined use, pregabalin reduced the antidepressant effects of amitriptyline, ketamine and diazepam while did not alter the antidepressant effect of fluoxetine. In addition, pregabalin decreased the anxiolytic effect of amitriptyline, did not change the anxiolytic effects of diazepam and fluoxetine when they were administered together. Furthermore an anxiolytic effect was observed when pregabalin was used in combination with ketamine.

Conclusions: Depressant effect was observed in all doses of pregabalin, while its anxiolytic effect was observed dose depended. In our study, the best combination of pregabalin(20mg/kg) was with fluoxetine. Pregabalin should be combined with SSRI group drugs in the treatment of depression when necessary.

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DIABETES INCUCED COGNITIVE IMPAIRMENT IS ASSOCIATED WIHT INCREASE OF NLRP3 AND NITROTYROSINE LEVELS IN THE HIPPOCAMPUS OF RATS

Busra Onar[1], Hale Sayan Ozacmak[2], Incı Turan[2], V.Haktan Ozacmak[2]

1Zonguldak Bulent Ecevit University, Institute of Heatlh Sciences, Department of Physiology, Zonguldak, Turkey. 2Zonguldak Bulent Ecevit University, Faculty of Medicine, Department of Physiology, Zonguldak, Turkey

hsayan@yahoo.com

Aims: Diabets mellitus is associated with impaired learning and memory. Neuroinflammation is a pathophysiological hallmark of diabetes which include production of cytokines. It was suggested that nitrative injury has been implicated in the pathophysiologic mechanism of diabetes. Nod-like receptor family pyrin domain-containing (NLRP) inflammasomes are important in the development of inflammatory response through production of IL-1β and IL-18. In the present study was aimed to examine the relationship between NLRP3, IL-1 β, nitrotyrosine levels and cognitive functions in diabetic rats.

Methods: The rats were randomly divided into 2 groups: control and diabetic. Diabetes was induced by a single intraperitoneal injection of 60 mg/kg of streptozotocin (STZ). Body weight and blood glucose were measured until euthanasia. Morris water maze (MWM) was used to evaluate the cognitive function in rats. Hippocampal NLRP3, IL-1 β and nitrotyrosine levels were measured. Statistically analyses were performed by Mann Whitney U test.

Results:The results showed that the elevated blood glucose was obseved in diabetic group. NLRP3 and nitrotyrosine levels were found to be increased in hippocampus of diabetic rats. There was no statsitical significance in the hippocampal IL-1β level with diabetes. In the MWM, diabetic rats spent more time to find the submerged platform when compared with control rats, implying a significant impairment of learning and memory, and this impairment was found to be statistically signifcant at day 5.

Conclusions: Our results indicate that STZ induced diabetes causes learning and memory impairment in rats probably by generating nitrosative stress and increasing NLRP3 level in the hippocampus.

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DOES DIPYRONE PRODUCE ANXIOLYTIC-LIKE EFFECTS IN MICE?

Ruhan Deniz Topuz, Ozgur Gunduz, Dikmen Dokmeci, Çetin Hakan Karadag, Ahmet Ulugol
Department of Medical Pharmacology, Faculty of Medicine Trakya University, Edirne, Turkey

ruhantopuz@gmail.com

Aims: Paracetamol has been shown to exert anxiolytic-like effects mediated by endocannabinoids via cannabinoid CB1 receptors. Dipyrone is an analgesic with similar effects to paracetamol rather than non-steroidal anti-inflammatory drugs. Involvement of central structures to its effects are long under debate, whereas recent findings suggesting contribution of cannabinoid CB1 receptors to its antinociceptive effect support this argument. Taken together, the purpose of this study was to investigate whether dipyrone possesses anxiolytic-like behavior; contribution of cannabinoid CB1 and CB2 receptors and TRPV1 receptors will be determined in case of observing any effect of dipyrone in anxiety tests.

Methods: After ethical approval, Balb-c mice effects of dipyrone (150, 300, 600 mg/kg, i.p.) were assessed in three-chamber social interaction, open-field, elevated plus-maze and rota rod tests. The cannabinoid CB1 antagonist AM251 (1 mg/kg i.p.), the CB2 antagonist SR 144528 (1 mg/kg i.p.) and the TRPV1 antagonist capsazepine (3 mg/kg i.p.) were going to be administered before dipyrone injections if any effect of dipyrone occurs. Statistical analysis is performed using ANOVA test.

Results: Dipyrone had no effect at any dose in behavioral tests (three-chamber social interaction, open-field, elevated plus-maze and rota rod tests). Therefore, dipyrone is not tested together with the cannabinoid CB1 and CB2 antagonists and the TRPV1 receptor antagonist.

Conclusion: Unlike paracetamol, dipyrone did not possess anxiolytic-like effects in mice. Discrepancies in experimental models and methodologies may be the reason of our results.

This study was accepted for publication in Cukurova Medical Journal.

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MOTOR SYMPTOMS MAY BE RELATED TO ELECTROPHYSIOLOGICAL CHANGES IN COGNITIVELY NORMAL PARKINSON'S DISEASE PATIENTS

Deniz Yerlikaya[1], Arzu Maharramova[2], Duygu Hünerli[1], Özgecan Kaya[2], Görsev G. Yener[2]

1Department of Neurosciences, Institute of Health Sciences, Dokuz Eylul University, Izmir, Turkey. 2Department of Neurology, Dokuz Eylul University Medical School, Izmir, Turkey

psk.denizyerlikaya@gmail.com

Aims: The aim of the study was to investigate resting-state EEG (rsEEG) changes in cognitively normal Parkinson's Disease (PD-CN) patients compared to healthy controls (HC).

Methods: Eyes-closed rsEEGs were recorded at baseline and one-year follow-up from 19 PD-CN patients and 20 demographically-matched HC. All participants underwent a detailed neuropsychological test battery. PD-CN patients were divided into two subgroups according to increase or decrease in the UPDRS motor scores over one-year. Delta (0.5-3.9 Hz), theta (4-7.9 Hz), alpha (8-13 Hz), alpha1 (8-10.4 Hz), alpha2 (10.5-13 Hz), beta (13-30 Hz), beta1(13-20 Hz) and beta2 (20-30 Hz) power were measured automatically from 12 electrodes. Separate repeated measures ANOVAs were performed for each power band.

Results: Repeated measures ANOVA did not reveal Group main effect or Group x Time interaction effect on the delta, theta, alpha, alpha1, alpha2, beta, beta1 and beta2 frequency bands. Subgroup analysis based on the change in the UPDRS motor scores revealed a Group main effect in theta power [$F(2,28)=3.448$, $p=0.046$], indicating increased theta power in PD-CN patients with increased UPDRS motor scores compared to healthy controls. However, the patients with decreased motor scores did not differ from patients with increased motor scores and HC.

Conclusions: The increased theta power is reported as an early sign of neurodegeneration. In the present study, although the cognitive profiles remain stable over one-year follow-up in PD-CN, the results indicate that the severity of motor symptoms may be associated with increased theta power.

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ANTIDEPRESSANT AND ANXIOLYTIC EFFECTS OF EUTERPE OLERECEA IN RATS AND COMPARISON WITH REFERENCE ANTIDEPRESSANT AND ANXIOLYTIC DRUGS

Cafer Yildirim[1], Sule Aydin[1], Basak Donertas[1], Setenay Oner[2], Fatma Sultan Kilic[1]

1Eskisehir Osmangazi University, Medical School, Department of Pharmacology, Eskişehir/ Turkey. 2Eskisehir Osmangazi University, Medical School, Department of Biostatistic, Eskişehir/ Turkey

y.cafer@gmail.com

Aim: Depression and anxiety are commonly seen phsyciyatric disorders and they negatively affect prognosis and treatment response of some other diseases. Inflammatory processess are suggested to be involved in the pathogenesis of depression. We aimed to investigate the antidepressant and anxiolytic effects of Euterpe Olerecea (EO) that is thougt to have antiinflammatory effects.

Methods: Wistar rats were randomly divided into 12-groups(n:8): Control, EO(30,100,300mg/kg), *amitriptyline(*20mg/kg), fluoxetine(20mg/kg), diazepam(5mg/kg), ketamine(5mg/kg) and their paired combinations with EO(100mg/kg) were administered orally. Forced swimming and elevated plus maze tests were used to investigate antidepressant activity and anxiolytic activity. In addition, locomotor activity of the rats were assessed. Tests were performed 1,5 hours later the drug administration. The results were analyzed with One Way ANOVA. $p<0.05$ was accepted as statistically significant.

Results: All doses of EO significantly reduced immobility time in forced swimming and time spent in closed arms in elevated plus maze tests. The effects of EO(100mg/kg) were similar to *amitriptyline,* ketamine, diazepam. But fluoxetine did not reduce immobility time and time spent in closed arms compared to control group. In all combinations, both immobility time and the time spent in dark were significantly compared to control while not significantly compared to EO(100mg/kg).

Conclusion: We suggest that EO, especially at a dose of 100mg/kg exerts antidepressant and anxiolytic effects comparable to reference antidepressant and anxiolytic drugs used in this study. However, the ineffectivenes of the reference drug fluoxetine on depression and anxiety tests may be attributed its acute administration.

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THE ROLE OF TASK-3 TWO-PORE POTASSIUM (K2P) CHANNELS IN CIRCADIAN ENTRAINMENT

Aiste Steponenaite[1], Tatjana Lalic[2], Lynsey Atkinson[1], Alistair Mathie[1], Zameel Cader[2], Gurprit Lall[1]

1 Medway School of Pharmacy, University of Kent, Chatham, UK. 2 Nuffield Department of Clinical Neurosciences, University of Oxford, UK

as2238@kent.ac.uk

The suprachiasmatic nucleus (SCN) is a principal circadian pacemaker synchronising our daily routines to environmental cues, such as the day/night cycle. The SCN relies on an endogenously generated electrical output rhythm as one of its timekeeping mechanisms. This consists of higher neuronal spontaneous activity during the day, which then silences during the night. Cellular excitation of the SCN is tightly regulated by two-pore domain potassium channels (K2P). These K2P channels play a role in establishing resting membrane potential and have been implicated in driving the excitability of SCN neurons.

Our study investigated the role of K2P TASK-3 channels in regulating circadian rhythmicity and light entrainment. We employed a TASK-3 knockout mouse model to assess alterations in SCN neuronal activity properties and the impact on output mechanisms.

Locomotor activity was increased in mice lacking TASK-3 in comparison to littermate controls. Moreover, behavioural deficits to light entrainment were evident in our KO model when animals were exposed to extreme light induced entraining stresses such as extended daylight photoperiods and 6-hour 'jet-lag' paradigms. In addition, TASK-3 KO mice were unable to respond in a dose-dependent manner to light induced behavioural clock resetting. At the molecular level, these mice exhibited reduced clock gene expression.

Taken together, we show that TASK-3, in the SCN, is a vital component for the homeostatic regulation of circadian entrainment. In mammals, alterations in SCN excitability through TASK-3 channels could affect seasonal adaptation to changing light-dark cycles and circadian re-entrainment to shifting time zones during transmeridian travel, thus impacting wellbeing.

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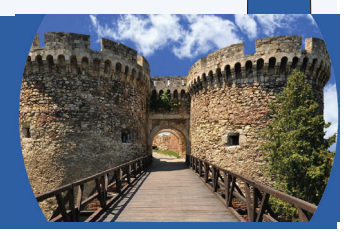

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EXPLORING THE MOLECULAR BASIS OF FEMALE-SPECIFIC RISK FOR ANXIETY AND DEPRESSION

Devin Rocks[1], Ivana Jaric[1], Heining Cham[2], Alice Herchek[1], and Marija Kundakovic[1]

1Department of Biological Sciences, Fordham University, Bronx, NY, United States, 2Department of Psychology, Fordham University, Bronx, NY, United States

as2238@kent.ac.uk

Aims: Females have twice the risk of developing anxiety and depression compared to males. Despite this, relevant animal studies focused on male animals, so the mechanisms underlying this sex-specific risk are unknown. To address this, we explored the role of fluctuating ovarian hormones and developmental stress in driving female-specific vulnerability to anxiety- and depression-related behaviors, and explored transcriptional and epigenetic changes that may underlie sex-specific behavioral phenotypes.

Methods: Male and female mice were subject to early-life maternal separation (MS) and/or adolescent social isolation, and as adults underwent anxiety- and depression-related behavioral tests (open-field, elevated-plus-maze, sucrose preference, forced-swim). To control for hormone status, female estrous cycle stage was checked using vaginal cytology. We employed targeted and genome-wide gene expression and epigenetic assays: qRT-PCR, Bisulfite-Pyrosequenicing, ATAC-seq in the ventral hippocampus, a region relevant for anxiety/depression.

Results: Early-life stress-exposed females showed increased depression-like behavior compared to males. Generally, within females, the high-estrogenic stage of the cycle was associated with decreased anxiety- and depression-like behavior compared to the low-estrogenic stage. This protective effect of estrogen was disrupted following early-life stress, as high- and low-estrogenic MS females exhibited no difference in anxiety-indices in the open-field test. Following developmental stress, we observed aberrant gene expression and DNA methylation in psychiatric-risk genes including Nr3c1 and Cacna1c in the ventral hippocampus. In the same region, we found estrous cycle- and sex-dependent chromatin organizational changes that we linked to behavioral phenotypes.

Conclusion: Our results indicate an important role for sex-hormone fluctuations and epigenetic dysregulation in female-specific susceptibility to stress-related depression and anxiety disorders.

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P419

THE ROLE OF CAV3.1 T-TYPE CALCIUM CHANNELS IN COGNITIVE PROCESSING MEDIATED BY THE SUBICULUM

Srdjan M. Joksimovic, Nicolas Busquet, Robert Valdez, Slobodan M. Todorovic

University of Colorado, Anschutz Medical Campus, Denver, CO, United States

srdan.joksimovic@ucdenver.edu

Aims: Our group previously showed that CaV3.1 isoform of T-type calcium channels (T-channels) is important for neuronal excitability and synaptic plasticity in the subiculum. Here, we aimed to investigate the role of subicular CaV3.1 T-channels in mediating cognitive functions.

Methods: Gene silencing was conducted by injecting AAV vectors expressing shCaV3.1 (AAV2-GFP-U6-mCACNA1G-shRNA) or control (scrambled shRNA) into the mouse dorsal subiculum (dSub). The knock-down (KD) confirmation was done by recording T-currents in GFP+/- subicular and thalamic neurons using voltage-clamp electrophysiology in acute brain slices. Next, we subjected dSub-specific KD and global CaV3.1 knock-out (KO) mice to open-field test, radial arm water maze (RAWM), and contextual fear conditioning (CFC). Finally, we recorded local field potentials (LFPs) from dSub of freely-moving wild-type (WT) and CaV3.1 KO mice.

Results: We detected a decrease of about 80% in T-current amplitude of GFP+ neurons (shCaV3.1 vs. control: P=0.001). Both dSub-specific KD and global KO mice showed impaired spatial learning in RAWM (genotype: P=0.023 and P=0.040, respectively). The magnitude of the freezing response in CFC was differentially affected in KD and KO mice. In vivo LFP recordings revealed a profound decrease in subicular beta and low gamma oscillations of KO mice during exploration of a novel environment. For example, both absolute and relative power in the 30-50 Hz frequency band were decreased for about 50% in KO mice (P=0.010 and P=0.043 vs. WT mice, respectively).

Conclusions: Our results show that CaV3.1 T-channels control certain aspects of learning and memory, most likely by regulating high-frequency oscillations in dSub.

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P420

NEURAL CIRCUITS FOR STOPPING RULES IN HUMAN DECISION MAKING

Mario Fific
Psychology Department, Grand Valley State University, Allendale, Michigan, USA
ficm@gvsu.edu

All human decision making models assume the three stages of cognitive operations: (1) the information search, (2) the stopping criterion that determines when the system should stop with the evidence accumulation, and proceeds with (3) the decision.

There is a strong parallel between the three stages of decision making models and functions of a single neuron. In a single neuron, summation of postsynaptic potentials is compared to a threshold value, which if exceeded triggers an action potential. The correspondence between the stages of decision models and the functions of neurons has allowed for new theoretical advances in providing better understanding of the functional organization of a neural system.

However, the recent behavioral evidence showed that human decision makers used several different stopping criteria (stage 2). For example, (a) some decision makers would stop when the sum of both positive and negative evidence would reach a certain value, (b) some would use streaks (runs) of the same type of evidence to stop, and (c) some would collect a fixed number of evidence units and then use the majority rule to determine a final decision. So far, the major advances in the area of neural modelling of decision making have been based on the application of rule (a).

The primary focus of the current research is to provide new theoretical ground for conceptualization of neural populations that can simulate various types of stopping rules, as observed in the human decision making behavior.

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P421

HIGHER CRITICISM OF NEURAL SIGNALS

Hamid R. Noori, Ekaterina Mitricheva, Rui Kimura, Nikos K. Logothetis, Farzad Fathi Zadeh
Max Planck institute for Biological Cybernetics, Tübingen, Germany

hamid.noori@tuebingen.mpg.de

Aims. In the analysis of neurophysiological data, numerous statistical tests are often needed to detect a small fraction of significant effects against a predominantly null background. Higher criticism (HC) is a method to determine whether there are any nonzero effects. We present an HC-based approach to robustly detect neurophysiological signals and large field deflections.

Methods. Monochromatic light (λ = nm) was used to induce neuronal response in lateral geniculate nucleus of six anesthetized adult male Wistar rats. Single neuron and multi-unit activity were recorded using a stereotaxically implanted microelectrode. The measured time-series were first transformed into an empirical process. For each time-step, the probabilities were calculated, sorted in increasing order and relabeled as We then calculate the HC value by the formulae:

A signal is detected, when the data is not locally normal distributed. Subsequently, -means clustering was applied on the set of and the related centroids (thresholds) were used to systematically sort the signals. The algorithm was tested on representative toy data and in vivo physiological measurements.

Results. Spikes and large field deflections were detected robustly and with high precision only based on the intrinsic data distribution. The presence of a signal is equivalent with a break in data Gaussianity.

Conclusions. Our findings demonstrate the efficiency and reliability of our HC-based method to characterize neuronal dynamics without prior manipulation of the data and in contrast to existing methods avoids the risk of losing information or inducing artificial features.

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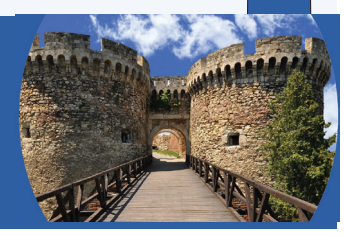

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P422

ARTIFICIAL NEURAL NETWORKS CAN RECOGNIZE PHYSIOLOGICAL STATES BY MEANS OF NONLINEAR FLUCTUATIONS FROM CARDIO-RESPIRATORY OSCILLATORS

Zoran Matić[1], Aleksandar Kalauzi[2], Mirjana M. Platiša[3] and Tijana Bojić[4]

1Biomedical Engineering and Technology, University of Belgrade, Belgrade, Serbia, 2Department for Life Sciences, Institute for Multidisciplinary Research, University of Belgrade, Belgrade, Serbia. 3Institute of Biophysics, Faculty of Medicine, University of Belgrade, Belgrade, Serbia. 4Laboratory for Radiobiology and Molecular Genetics-080, Institute for Nuclear Sciences Vinča, University of Belgrade, Belgrade, Serbia

z.matic157@yahoo.com

Aims. Nonlinear fluctuations of R-R interval (RRI) and respiration mostly reflect subtle neural drive from ventrolateral medulla. They are more sensitive to changes of physiological conditions than properties from the linear domain. Artificial neural networks (ANN) and nonlinear parameters of RRI are used successfully as classifiers of various cardiac pathophysiological states, traditionally registered in supination with spontaneous breathing. Monitoring techniques revealed that physiological conditions have influence on correct RRI signal interpretation. Our research aimed to define the pattern of four physiological conditions by means of ANN, RRI and respiratory nonlinear parameters.

Methods. Using Biopac MP100 system (1000 Hz sampling rate) we made acquistion of RRI and respiration signal from 20 healthy subjects in 4 physiological conditions (supine/standing vs. spontaneous/slow breathing). Nonlinear parameters (multiscaling entropy and fractality) were estimated with Matlab algorithm. In this way we used 6 parameter sets of 80 values as inputs to ANN classifiers constructed in Neuroph software. Outputs of ANN classifiers were 4 physiological states. We selected 60 % of whole dataset to train ANN classifier, and the rest 40 % for testing.

Results. After optimisation of architecture and learning parameters, ANN classifier with 18 neurons in each of two hidden layers had the best performance of 81 % classification accuracy.

Conclusion. ANN classifier based on ECG and respiratory pattern recognition could be useful for detecting physiological states (laying, standing, spontaneous or slow breathing etc) promoting cardiorespiratory operational pattern as crucial for future potential interpretation of holter recording or signal monitoring in patient care units.

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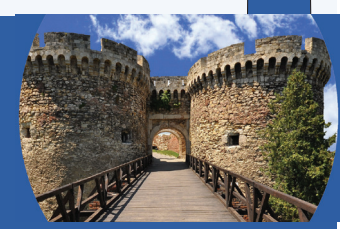

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LOW LATENCY EEG PHASE ESTIMATION FOR REAL-TIME EEG PHASE-LOCKED STIMULUS PRESENTATION IN HUMANS

Dominik Brügger, Thomas Ferrazzini, Mathias Abegg

Department of Ophthalmology, Inselspital, Bern University Hospital and University of Bern, Switzerland

dominik.bruegger@insel.ch

Aims:To develop a system for EEG phase-locked stimulus presentation, with low latency, using commercial hardware certified for research in humans. To facilitate the study of phase dependence on visual responses.

Methods: A computationally optimized method for phase estimation, based on sine-fitting to the raw EEG-traces, is used to estimate and predict the phase with minimal latency. The algorithm is developed in Matlab, and can be used in combination with Psychtoolbox, and Lab-Streaming-Layer (LSL), it is fully compatible with Matlab Coder for C/C++ code generation. Explicit precomputation of coefficients allows to significantly reduce the number of computations needed during runtime.

Results: The performance of the phase-locking algorithm has been evaluated in a theta (4-8Hz) selective visual task, where it achieved a good phase selectivity with an inter-trial phase coherence (ITC) of 0.348(0.100) (mean(SD)), despite the low signal to noise ratio in the theta band. Calculation of phase and mean-squared-error for 41 discrete frequencies in a 1001 samples long sequence requires 129us(10.97us) (mean(SD)), using Matlab 2019a on a desktop computer (i7-8700K @4.7GHz).

Conclusions: By eliminating the need for digital filters and their associated group delay our algorithm allows to estimate the phase of online EEG signals with only a short computation dependent lag. This allows to measure the effect of oscillatory phases on the visual response.

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P424

TIME LAPSE IGG-INDUCED CALCIUM SIGNALING ANALYSIS FOR ALS DIAGNOSIS

Çapar A[1], Dursun G[2], Korenić A[3], Bijelić D[3], Radenović L[3], Özkaya U[2], Kerman BE[4] , and Andjus P[3]

1Istanbul Technical University, Turkey, 2Süleyman Demirel University, Isparta, Turkey, 3Faculty of Biology, University of Belgrade, Serbia, 4Istanbul Medipol University, Turkey

capar@itu.edu.tr

We have shown that IgG from sera of ALS patients compared to control IgG induce calcium transients in cultured rat astrocytes. Our aim was to develop automated diagnostic screening for calcium signaling in order to classify ALS IgG.

The first step is segmenting the cell nuclei's on the maximum intensity projection image of time-lapse image stack by adaptive histogram equalization and thresholding. Average intensities of cell regions are calculated for each nuclei and each time-lapse image. Hence, one dimensional average intensity signal, is created for each cell along the time scale, forming the "cell trace". To form the input of the supervised classifiers these cell traces are placed in the feature images row by row. Thus, feature images have M x N dimensions, where M is the total number of cells and N is the number of images in the time-lapse image stack. The indexes of the rows are changed randomly and new images are created as to become independent from the order of the cells. This augmentation process is very important both to become invariant from cell order and to efficiently collect the adequate number of image samples, all required to train supervised classifiers. Support Vector Machines are utilized to classify feature images for ALS diagnosis. The study was performed on 10 ALS and 5 non-ALS patients.

It will be demonstrated that the proposed method is appropriate for automation of ALS diagnosis with the IgG calcium imaging setup.

Acknowledgment: This study was supported by H2020-MSCA-RISE project 778405 "AUTOIGG"

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P425

INVESTIGATION OF TRANSCRIPTIONAL REGULATORY NETWORK OF ETS FAMILY TRANSCRIPTION FACTORS - A SYSTEMS BIOLOGY APPROACH

Yigit Koray Babal, Isil Aksan Kurnaz

Gebze Technical University, Department of Biotechnology, Gebze, Kocaeli, Turkey

ykbabal@gtu.edu.tr

Aims: E-twenty-six (E26 Transformation Specific, ETS) transcription factor superfamily is a one of the biggest transcription factor families that can be seen only metazoan lineage. ETS family plays a critical role in many biological processes such as differentiation, cell proliferation, apoptosis and cancer progression, among many others, through transcriptional regulation. Our aim is to investigate intrafamilial regulation network of ETS Family using transcriptomics studies in the literature.

Methods: In this study, initially promoter analysis was performed to predict putative TF binding site on the promoters of selected ETS members. Then mathematical modeling of intrafamilial regulatory network of ETS Family members was constructed using microarray data in the literature with COPASI software. The network behavior was investigated under conditions that simulate overexpression of the ETS members Elk1 and Pea3, parallel to previous experimental studies in our laboratory. On the other hand, protein-protein interaction network was predicted by using the integration of whole human protein-protein interaction (PPI) network and transcriptomics data to construct PPI subnetwork of ETS members in human.

Results: In our laboratory, we showed that there is distinct intrafamilial regulation network of ETS Family transcription factors that can mediate different biological processes. Elk1 and Pea3 in particular have critical role in this regulatory network with respect to differentiation decisions during development.

Conclusions: We have used a systems biology approach to investigate regulatory network of ETS members and verify previous findings in our laboratory. Integration of transcriptomics data with PPI network proved to be a useful method to analyze such transcriptional networks.

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P426

A HIERARCHICAL SPIKING NEURAL NETWORK THAT SOLVES THE "CATCH-THE-FOOD" TASK WITH THE UTILIZATION OF GENETIC ALGORITHM

Mustafa Kerem Kurban, Abdurrezak Efe, Seymur Cahangirov
Bilkent University, Ankara, Turkey

keremkurban@hotmail.com

Aims: Building an Izhikevich model of spiking neural network which teaches itself to solve a particular task in an unsupervised manner using a genetic algorithm. Revealing time locked and synchronous neurons using reshuffling of spike events. Utilizing of stochastic resonance in neuronal networks to boost the task performance.

Methods: Python (3.7)

Results: We analyzed the properties of a model neural circuitry built from 1000 Izhikevich neurons and incorporate genetic algorithm to maximize the performance of this system with an easy task of grabbing an object that it sees. The objects are present in a two-dimensional computational universein in which the vision is one dimensional. The system eventually maps this one-dimensional input into a two-dimensional mind map. This is shown by analyzing the raster plots with two methods we developed to map the firing patterns into an understandable flow chart. Furthermore, we searched for the optimal spike noise ratio to get the stochastic resonance phenomenon and boost our the task performance.

Conclusions: We have built a new method to find out the time-locked neurons from raster plots and have shown that the model we have built can solve the task in a supervised manner. In the further studies, we intend to investigate the neural engrams formed within the network of successful candidates and what information they encode to solve the task.

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P427

COMPUTATIONAL APPROACHES TOWARD TYROSINE RECEPTOR KINASE B AGONISTICS

Muhammed Fatih Karakaya, Cagatay Ozan Karabulut
Eskisehir Osmangazi University, Faculty of Medicine, Department of Physiology

qhosthat@gmail.com

Aim: Our aim is Computational approaches to ligand designs on tyrosine receptor kinase B (NTRK2), which are frequently encountered in neurodegenerative diseases

Methods: NTRK2 gene primer sequence has been imported from Ensembl [ENST00000277120.7]. Tyrosine receptor kinase B binding domain [pdb:1WWB] was used as a template for NTRK2 homology modeling. To get ready for analysis, proteins have been prepared such as missed Hydrogens in the raw state of the protein was added in the first stage. The next step is arranging waters or protons' geometries and also adding hydrogen bonds etc. Later step carries on with two steps; optimization of functional groups' states and minimization of the structure, respectively. This prepared protein used as a template for NTRK2 gene homology modelling. After modelling of the receptor, binding sites were detected by active sites. Finally, the pharmacophore model was developed using receptor cavity for further analysis.

Results: Ligand modelling and binding scores were performed and determined based on this hypothesis. 14 compounds were generated by 5 distinct pharmacaphore model. Generally good docking scores were observed.

Conclusion: Residues and types of interaction in which the ligands interacted were indicated. General binding capacity is through H bonds and pi-cation interactions. When ring conformation is disrutped, docking capacity significantly reduces.

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TRANSCRIPTOMIC ANALYSIS OF POST-MORTEM BRAAK-CLASSIFIED PARKINSON'S PATIENTS

Cagatay Ozan Karabulut, Muhammed Fatih Karakaya
Eskisehir Osmangazi University, Faculty of Medicine, Department of Physiology

cagatayozank@gmail.com

Aim: Parkinson's disease (PD), known for the death of dopaminergic neurons and associated motor dysfunction, is a common neurodegenerative disease. Braak Staging is used to classify the degrees of Parkinson's and Alzheimer's diseases. The study was conducted for the investigation by analyzing significant gene changes in PD patients classified according to Braak Staging method after diagnosis.

Methods: In this study, Data was collected from a database (Gene Expression Omnibus). It contained 6 Post-mortem control group (4 male,1 female), 4 Post-mortem Braak-3 PD(3 male,1 female), 4 Post-mortem Braak-4 group (2 male, 2 female) substantia nigra regions microarray data from classified PD tissue samples. Data sets were analyzed by NCBI Geo2R tool and genes which showed significant differences were selected and their major common characteristics were analyzed by using g:Profiler. Also, ClustVis tool was used for the cluster analysis. Protein-protein interactions were determined and mapped according to their level of significance by using STRING database. These protein-protein interactions were visualized and calculated with the help of Cytoscape.

Results: After the Geo2R analysis, it was observed that the most common molecular function of these genes was protein binding. Other common biological processes were neuron development, cell morphogenesis involved in neuron differentiation and axogenesis. We observed significant changes in disease groups.

Conclusion: In this study, significant changes were observed in genes and related pathways of classified PD stages. These results can play a role in the determination of the stage of the disease at the gene level.

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A COMPUTATIONAL MODEL OF BASAL GANGLIA NETWORK INCLUDING VENTRAL STRIATUM

Rahmi Elibol, Neslihan Serap Şengör
Istanbul Technical University, Electronics and Communication Engineering
rahmielibol@itu.edu.tr

Aims: Though there are various computational models of basal ganglia networks, few considered accumbens nucleus which is especially substantial in limbic circuit. Here, a computational model of basal ganglia limbic network is modeled using point neurons, where direct, indirect and hyper-direct pathways are included.

Methods: In the model, pyramidal and interneurons of cortex, fast spiking neurons of globus pallidus and subthalamic nucleus are considered along with rebound bursting neurons of thalamus. Accumbens nucleus is modeled in more detail, where different properties of medium spiny neurons (MSN) and interneurons of core and shell parts are considered, especially taking into account the different dopamine receptors.

Results: The behavior of the Basal Ganglia is shown in Figure 1. When there is a stimulus activating cortex while no reward information from VTA, D2 type neurons produce more spikes than D1 type neurons. If there is a reward signal, whether the signal from cortex is or not weakened, the activity of D1 type neurons are more than D2 type neurons.

Conclusions: The simulations results obtained for the proposed model show that when the effect of a stimulus is projected through cortex, D2 type MSNs became more activated than D1 type MSNs due to their biophysical properties, so enabling the indirect pathway to be dominant over direct pathway and inhibiting thalamus. On the other hand, when the dopaminergic cells in the ventral tegmental area are activated, the activity of D1 type MSNs are aroused, making direct pathway activated, so disinhibiting thalamus.

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MODULATION OF EXCITATION/INHIBITION BALANCE IN A HUMAN INDUCED NEURONAL MODEL

JR van Rhijn[1,3], B Mossink[2,3], J Bak[1,3], N Nadif Kasri[1,2,3], D Schubert[1,3]

1 Department of Cognitive Neuroscience, Radboudumc, Nijmegen, Netherlands;
2 Department of Human Genetics, Radboudumc, Nijmegen, the Netherlands: 3 Donders Institute for Brain Cognition and Behaviour, Nijmegen, Netherlands

Jon-Ruben.vanRhijn@radboudumc.nl

Healthy brain function depends on a fine-tuned balance between activation by excitatory (E: glutamatergic) and modulation by inhibitory (I: GABAergic) inputs. Disruption of this E/I balance underlies many neurodevelopmental disorders (NDDs). It is possible to functionally investigate NDDs by generation of human induced neurons (iNeurons) from human induced pluripotent stem cells (hiPSCs). However, many protocols that generate iNeurons provide either only excitatory neurons or a heterogeneous population in which the amount of excitatory and inhibitory neurons is neither defined nor controlled. This hampers the use of iNeurons to investigate functional aspects of the E/I balance. Furthermore, little is known about the maturation of GABAergic iNeurons and whether networks composed of glutamatergic and GABAergic iNeurons receive functional inhibitory control. We therefore set out to generate GABAergic neurons that display mature GABA release and inhibitory control at the network level when cocultured with glutamatergic iNeurons.

Here, we developed and characterized a novel protocol to generate a pure population of GABAergic iNeurons. HiPSCs were differentiated into GABAergic iNeurons independently, but cocultured with glutamatergic neurons in a 20:80 (GABA:glutamate) ratio to generate composite networks. This is necessary, because GABAergic neurons are unable to mature without excitatory drive. We first validated the presence of GABAergic and glutamatergic iNeurons in our cocultures based on molecular markers for neuronal identity. Next, we assessed the maturation of GABAergic and glutamatergic iNeurons in coculture. After 49 days in vitro (DIV), both iNeuron types displayed mature intrinsic electrophysiological properties. Extensive functional network integration was apparent as all recorded iNeurons received ongoing glutamate and GABA-mediated spontaneous postsynaptic inputs. To investigate if GABA mediated responses in our network become hyperpolarizing during development, we measured the reversal potential of chloride at the single-cell level, as well as GABAergic network control at the population level with micro-electrode arrays (MEA). Our data show that the chloride gradient mediates excitatory GABAergic postsynaptic responses until DIV35. However, between DIV35 and DIV49, a shift in the chloride gradient resulted in a change from de- to hyperpolarizing GABAergic responses in the glutamatergic iNeurons. Lastly, changing the percentage of inhibitory neurons present in the coculture on MEA resulted in tuning of the network burst duration, which decreased with increasing inhibitory:excitatory neuron ratio. This novel protocol enables us to characterize inhibitory control in composite E/I cocultures, which will aid investigation of NDDs in which E/I balance is disturbed.

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FUNCTIONAL TESTS AND THEIR IMPORTANCE IN THE EVALUATION OF RECOVERY AFTER PERIPHERAL NERVE INJURY

R.D. Alvites[1,2], M.V. Branquinho[1,2], S. Geuna[3], A.S.P. Varejão[4,5] , A.C. Maurício[1,2]

[1]Departamento de Clínicas Veterinárias, Instituto de Ciências Biomédicas de Abel Salazar (ICBAS), Universidade do Porto (UP), Porto, Portugal. [2]Centro de Estudos de Ciência Animal (CECA), Instituto de Ciências, Tecnologias e Agroambiente da Universidade do Porto (ICETA). [3]Department of Clinical and Biological Sciences, and Cavalieri Ottolenghi Neuroscience Institute, University of Turin, Ospedale San Luigi, Turin, Italy. [4]Departamento de Ciências Veterinárias, Universidade de Trás-os-Montes e Alto Douro (UTAD), Quinta de Prados, Vila Real, Portugal. [5]CECAV, Centro de Ciência Animal e Veterinária, Universidade de Trás-os-Montes e Alto Douro (UTAD), Quinta de Prados, Vila Real, Portugal.

ruialvites@hotmail.com

Peripheral nerve Injuries (PNI) are a common occurrence in both human and animal patients. These nerve damages trigger serious functional changes at the motor, sensorial and autonomic levels, seriously affecting the physiological performance. The spontaneous axonal regeneration process, although possible, is extremely complex and is rarely achieved without some level of therapeutic intervention. Animal models are important to mimic and investigate the mechanisms of nerve regeneration associated with the application of different therapeutic options.

Although histomorphometric repair and reorganization is important from a regenerative point of view, functional recovery in its motor and sensory components will always be the ultimate goal of nerve regeneration stimulation. Therefore, the selection and establishment of appropriate evaluation methods should be prioritized in the assessment of regeneration and functional recovery after PNI in animal models. It is important to understand the stages in which the process of nerve regeneration is divided and to select the most appropriate method for each one, allowing a correct interpretation of results. The three phases that should be considered are axonal regeneration, reinnervation of target organs and general functional recovery.

Assessment methods should always be applied in order to achieve a quantitative determination for each stage, investigating the recovery of all types of function commonly lost in nerve damages (motor, sensory and autonomic). The objective of this work is to summarize the types of functional evaluation methods available and most commonly described in the scientific literature, their advantages and main disadvantages and what should be improved within this topic in the future, focused in the rat and ovine animal model.

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GEMININ IS ESSENTIAL TO PROTECT NEUROEPITHELIAL CELLS FROM REPLICATION STRESS

Argyro Kalogeropoulou[1], Marianna Iliadou[1], Maria Mougkogianni[1], Zoi Lygerou[2], Stavros Taraviras[1]

1 Department of Physiology, School of Medicine, Patras University, Patras, Greece;
2Department of General Biology, School of Medicine, Patras University, Patras, Greece

iroumba@gmail.com

Aim: Perturbations in the regulation of DNA replication during early development lead to impaired cell proliferation and reduced cell numbers resulting in growth failure. Defective DNA replication licensing during embryonic development causes a severe type of primordial dwarfism with microcephaly, known as Meier-Gorlin Syndrome (MGS)1ORC4, ORC6, CDT1, and CDC6. Mutations in these genes cause disruption of the origin of DNA replication initiation. To date, only an autosomal-recessive inheritance pattern has been described in individuals with this disorder, with a molecular etiology established in about three-fourths of cases. Here, we report three subjects with MGS and de novo heterozygous mutations in the 5′end of GMNN, encoding the DNA replication inhibitor geminin. We identified two truncating mutations in exon 2 (the 1(st. Intriguingly, there is a group of MGS patients that carry mutations in the gene of Geminin, a known inhibitor of DNA replication. Previous studies have shown that inactivation of Geminin causes re-replication, a source of replication stress and subsequent DNA damage-induced apoptosis2. Our aim is to investigate the role of Geminin in the regulation of DNA replication and the importance of this mechanism in neural stem cells during development.

Results: We have generated a mouse model in which Geminin is specifically inactivated from the early telencephalon. We demonstrate that upon deletion of Geminin the embryos exhibit a dramatic decrease in the size of the developing cortex. Neuroepithelial cells exhibit increased DNA damage after Geminin deletion, resulting in gradual loss of stem cells pool. Interestingly, when Geminin is deleted from the apical Radial Glia cells of the developing cortex (E11.5) we do not observe any severe brain malformations or signs of DNA damage. To shed light in the differential regulation of replication between the distinct populations of NSCs, we performed analysis of MCMs loading and DNA fibers of NSCs derived from mouse embryos of different developmental stages.

Conclusions: Our analysis gives a new insight into the protective role of Geminin in early cortical neural stem cells by maintaining genomic stability and proper cortical development.

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P433

PLANT LEARNING: REPLICATING CUTTING EDGE SCIENCE EXPERIMENTS IN THE HIGH SCHOOL BIOLOGY CLASSROOM

Jessica Shin[1,2], Stanislav Mircic[1], Etienne Serbe[1,3], Gregory J. Gage[1]

1Backyard Brains, Ann Arbor, Michigan, United States;
2Fairmont Preparatory Academy, Anaheim, CA, United States;
3Max Planck Institute of Neurobiology, Martinsried, Germany

jshin@fairmontschools.com

Aims: Biology curricula in high schools could be improved using cutting edge science. Most schools do not have access to costly research equipment, labs and hands-on activities in the biology classroom.

Plant learning, a topic recently published on in scientific journals, is an intriguing concept that still does not have full scientific consensus but can easily be studied in the K12 classroom. In this project, we show that students can replicate science experiments published in Nature in order to learn how to perform a scientific experiment and how to draw a conclusion from self-collected data.

Methods: Students are given the research question, "Can plants learn to associate?" They are then exposed to different studies that have been conducted to answer the question. They chose to replicate or modify them over a course of 4 weeks, and took a pre- and post-survey on scientific methods and attitude towards science.

Results: Students reported increased understanding of the research process and study design. They reviewed one anothers' study results and the discussions improved scientific concepts and practices.

Conclusions: Replicating science experiments is an excellent way for students to experience science by doing. They are able to compare their projects to published studies, determine scientific validity, and understand research planning, design, data collection, and analysis. The undetermined nature of some research questions also reflects the ongoing and sometimes ambiguous processes of science.

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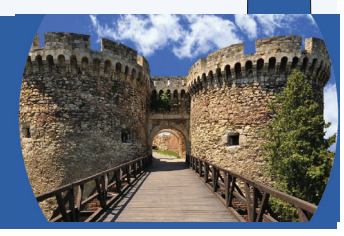

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SHORT-TERM HYPOXIA DIFFERENTLY AFFECTS EXCITATORY AND INHIBITORY NEUROTRANSMISSION IN VISUAL RETINOCOLLICULAR CIRCUIT

Hanna Dumanska, Nickolai Veselovsky

Bogomoletz Institute of Physiology, National Academy of Science of Ukraine, Department of Neuronal Networks Physiology, Kyiv, Ukraine

doomannya@gmail.com

The visual system is extremely sensitive to hypoxia due to its energy demands. Different types of visual system lesions are often mediated by a short- or long-term hypoxia. Retinocollicular projections form the initial level of visual signal transmission from the retina to the subcortical visual center (superficial superior colliculus, SSC). Structural and functional responses to hypoxic injury in retinocollicular projections were demonstrated using functional magnetic resonance imaging. Whereas, hypoxia-induced effects on this neurotransmission were not previously investigated.

Using the paired patch-clamp technique, we studied the effects of short-term hypoxia on retinocollicular synaptic transmission in an originally-developed coculture of dissociated retinal cells and SSC neurons. Pharmacologically isolated NMDA–, AMPA– and GABAA–mediated postsynaptic currents (PSCs) were evoked in SSC neurons by generation action potentials in presynaptic retinal ganglion cells. Spontaneous and miniature PSCs were recorded in SSC neurons in the absence of presynaptic stimulation.

Short-term (up to 5 min) hypoxia induced long-term potentiation of NMDA transmission, long-term depression of GABAA neurotransmission and temporary suppression of AMPA transmission. Also, we observed hypoxia-induced reduction of voltage-dependent magnesium blockade of evoked NMDA response. Evoked, spontaneous and miniature postsynaptic currents were analyzed in terms of a binomial model. This analysis revealed that hypoxia acts mainly presynaptically on excitatory neurotransmission and both pre →and postsynaptically on inhibitory retinocollicular transmission. Thus, we showed for the first time hypoxia-induced bidirectional long-term plasticity of the retinocollicular synaptic transmission. The results obtained reflect the electrophysiological basis of hypoxia-involved pathological lesion of the retinocollicular pathway.

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THE APPLICATION OF COMPUTATIONAL METHODS TO THE ANALYSIS OF LONGFIN INSHORE SQUID PARALARVAE BEHAVIOR

Christy Warden[1], Jonathan Tang[2,3], Aljoscha Leonhardt[4], Eric Edsinger[2], Etienne Serbe[1,4], Gregor J. Gage[1]

1Backyard Brains, Ann Arbor, MI, United States;
2Marine Biological Laboratories, Woods Hole, MA, United States;
3Columbia University, New York, NY, United States;
4Max Planck Institute of Neurobiology, Martinsried, Germany

cew4@rice.edu

Aims: As genetic tools evolve, there is an increased interest in studying intelligent invertebrates to understand the nervous system. The squid Doryteuthis pealeii is widely used in summer research, however the life cycle has not been closed to allow for year-round studies. Little is known about the early life of these squid and the methods that hatchlings use to survive past the paralarval developmental stage. It is suspected that the squid navigate to optimum feeding locations using light indicators, as they demonstrate photo- and geotaxicity.

We seek to develop lightweight computational and image processing methods to quickly analyze and quantify the specifics of these behaviors. Through these methods we set out to reproduce results demonstrated by previous studies on the species as well as elucidate the potential for such methods to be used in the analysis of other similar species and behaviors.

Methods:Squid were raised in a controlled laboratory environment and hatchlings were recorded every 6-12 hours. Squid were recorded during different light stimuli at the age of < 24 hours and > 48 hours. The videos were analyzed using a Matlab program which subtracted the background and dilated the squid forms. The program segmented the tank into equally stacked, vertical sections and the population's location was estimated by averaging the white pixels occupied by squid hatchlings.

Results: Analysis of Doryteuthis pealeii under these methods confirmed findings that hatchlings prefer low light levels. Additionally, our experiments unraveled age distinctions in these behaviors.

Conclusion: Lightweight image processing and graphing methods provide new opportunities to easily understand the phototaxic and geotaxic behavior of animals whose minute movements are not obvious from simple observation. The use of such methods could improve future studies.

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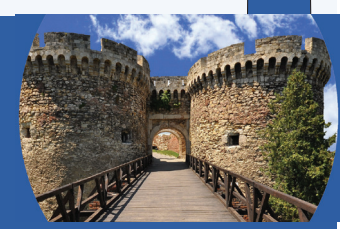

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P436

A LOW-COST APPROACH TO RECORDING EVENT-RELATED BRAIN POTENTIALS IN THE CLASSROOM

Kylie Smith[1,2], Stanislav Marcic[1], Nick Ristow[1], Dylan Miller[1], Marcio L. M. Amorim[1], Zach Reining[1], Timothy C. Marzullo[1], Etienne Serbe[1,3], Gregory J. Gage[1]

1Backyard Brains, Ann Arbor, MI, United States;
2Michigan State University, East Lansing, MI, United States 3Max Planck Institute of Neurobiology, Martinsried, Germany

smit2046@msu.edu

Aims: Neuroscience classrooms could benefit from engaging students laboratories that focus on hands-on techniques used in modern neuroscience investigations. Therefore, we aim to develop a low-cost electroencephalogram (EEG) capable of recording a well-known event-related potential that occurs in response to novel stimuli - the P300. This technology is designed with the intention to incorporate it into the classroom, giving students hands-on experience collecting and interpreting neuroscientific data.

Methods: Recording and ground electrodes attached to a Heart and Brain SpikerBox (Backyard Brains, Ann Arbor, MI) are placed over the Pz location and temple of participants, respectively. Participants listen to a series of two tones, recording each appearance of the less frequent tone - the "oddball" tone. The signals recorded from the Heart and Brain SpikerBox were analyzed by averaging the EEG around "tone" and "oddball" cue onset. The noise distribution of the EEG was determined using a Monte Carlo simulation.

Results: The average EEG signal around the "oddball" cue rose above the 95% confidence interval of the Monte Carlo simulation around 300ms after onset. This is consistent with a P300 signal. Notably, the "tone" signal did not significantly deviate from noise. We successfully recorded from 12 participant's parietal lobe, and found that 7 had a reliably observed P300 signal.

Conclusions:Low-cost commercial technology can record event-related potentials from the brain of a participant in minutes. This solution could be readily incorporated into a classroom, giving students hands-on experience in collecting and interpreting neuroscientific data.

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ON THE DEVELOPMENT OF MIXED COMPUTATIONAL AND PHYSIOLOGICAL NEUROSCIENCE TOOLS FOR EDUCATION

Isidora Kraguljac[1,2], Marcio L. M. Amorim[3], Zachary Reining[3], Etienne Serbe[3,4], Thomas Baden[5], Gregor J. Gage[3]

1Backyard Brains Beograd, Novi Beograd, Serbia;
2University of Belgrade, Belgrade, Serbia;
3Backyard Brains, Ann Arbor, MI, United States;
4Max Planck Institute of Neurobiology, Martinsried, Germany;
5School of Life Sciences University of Sussex, Brighton, United Kingdom

m44_2017@stud.bio.bg.ac.rs

Aims: Physiological recordings of spiking neurons have been shown to be beneficial in the neuroscience classroom. However, when learning neuroscience it is often important to understand computational or mathematical ways of describing neurons and axons (e.g. Nernst equations, Hodgkin and Huxley models). We evaluated the Spikeling (an Arduino-based computational neuron; Baden et al., 2018) to see if it could complement our lessons using physiological neurons of the cockroach leg.

Methods: High school and university students were used to determine the feasibility and usefulness of lessons. Groups of three students were given a modified Spikeling and a Neuron SpikerBox with a cockroach leg. They collected data, compared results and discussed them. Afterwards, there was an anonymous survey that allowed students to evaluate the usefulness of the Spikeling lessons, and its usefulness in understanding the biological neurons observed.

Results: Students had an opportunity to intuitively learn about physiology and compare data collected from a virtual neuron vs real neuron. Hands-on experience with computational tools enabled the students to better understand the theoretical concepts in electrophysiology and learn experimental methodology in science in general. The survey showed that students predominantly considered Spikeling lessons more useful than solely physiological experiments.

Conclusion:Using both physiological and computational tools to describe neural activity has shown to promote better understanding and more intuitive learning. The computational neuron provides a spectrum of different examples that is more difficult to achieve using physiological models. Introducing more complex concepts was facilitated by learning about the basics through experience.

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P438

AN ELECTROPHYSIOLOGICAL INVESTIGATION OF POWER-AMPLIFICATION IN THE BALLISTIC MANTIS SHRIMP PUNCH

Daniel J. Pollak[1,2], Kathryn D. Feller[3,4], Étienne Serbe[1,5], Stanislav Mircic[1], and Gregory J. Gage[1]

1Backyard Brains, Ann Arbor, MI, United States;
2University of Massachusetts Amherst, Amherst, MA, United States;
3Department of Physiology, Development and Neuroscience;
University of Cambridge, Cambridge, United Kingdom;
4Grass Foundation Grass Laboratory, Marine Biological Laboratories, Woods Hole, MA, United States;
5Max Planck Institute of Neurobiology, Martinsried, Germany

danpollak23@gmail.com

Aims: Mantis shrimp hunt with one of the fastest movements in the natural world. Their power-amplified strike accelerates their raptorial appendages with extreme speed. Other arthropods such as trap-jaw ants and grasshoppers also use power-amplified movements to hunt and evade predation. We present a template laboratory exercise for studying the electrophysiology of power-amplified limb movement in arthropods, with a specific focus on mantis shrimp strikes. The goal of this exercise is to empower students to build and perform challenging experiments to understand a complex biological principle. Electrophysiology in arthropods is generally terminal. We set out to design a low-cost, chronic setup for recording EMGs in arthropods.

Methods: Students learn the principles of electrophysiology by fabricating EMG probe systems and performing implant surgeries. Students then record EMGs while presenting behaviorally relevant stimuli to generate strikes. Analyses of the EMG data allow students to characterize mantis shrimp movements and compare them with other species.

Results: Students learn to handle the animals, make and implant electromyogram (EMG) probes, and finally perform experiments. Additionally, we devised a simple, low-cost EMG probe suitable for long-term studies in mantis shrimp.

Conclusions: This laboratory exercise allows students to develop methodology, problem-solving and inquisitive skills crucial for pursuing science. This integrative approach introduces the concept of power-amplified neuromuscular control and allows students to fabricate their instruments.

Our EMG probes allow for chronic implantations of electrodes in arthropods such as mantis shrimp. This approach to experimentation is not in widespread use and presents opportunities for new kinds of insights.

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STUDY WHILE YOU SLEEP: AN ELECTROENCEPHALOGRAM INVESTIGATION OF TARGETED MEMORY REACTIVATION

Joud I. Mar'i[1], Robert Zhang[2], Stanislav Mircic[1], James W. Antony[2], Kenneth A. Norman[2], Matthias Meier[3], Etienne Serbe[1,3], Gregory J. Gage[1]

1 Backyard Brains, Ann Arbor, Michigan, United States;
2 Princeton Neuroscience Institute, Princeton University, Princeton, New Jersey, United States;
3 Max Planck Institute of Neurobiology, Martinsried, Germany

mari22j@mtholyoke.edu

Aims: Memories are not static, they get stabilized from short to long term through the process of memory consolidation in the hippocampus. Therefore, their storage is constantly updated via reactivation of previously learned content specifically during NREM - Slow Wave Sleep. This sleep-dependent preferential consolidation can be artificially enhanced using TMR - Targeted Memory Reactivation. This technique can use auditory cues associated with learning to reactivate relevant neural representations reflected by certain hippocampal firing patterns. Here, we develop a low-cost open-source lab experiment to demonstrate this method using a self-designed iOS application and EEG recording hardware and software.

Methods: Twelve human subjects learned to play the iOS sound-associated spatial memory game and were tested before sleep. Subjects took a 90 minute nap while recording their EEG. Once SWS was detected, half of the sound cues from the game were re-played while the other half was substituted with novel sounds. Subjects were asked to play the memory game again upon waking up.

Results: For trials in which the sounds were cued during Slow Wave Sleep, subjects showed significantly better spatial recall after sleep than trials with the novel uncued sounds. TMR seems to effectively bias spatial associative memory consolidation, by altering the level of forgetness more than providing pure gain of remembering cued images better.

Conclusion : This DIY experiment of the TMR technique could be suitable for further applications in learning, teaching, and user self-led investigations to test various parameters of TMR and cueing at different sleep stages for instance.

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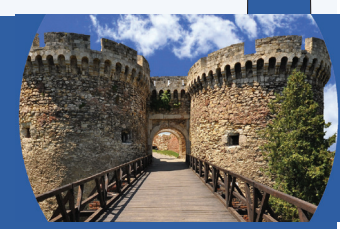

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P440

MOLECULAR ARCHAEOLOGY OF THE HUMAN BRAIN

Joanna Kaczanowska[1], Florian Ganglberger[2], Bence Galik[3], Andreas Hess[4], Yoshan Moodley[5], Katja Bühler[2], Wulf Haubensak[1]

1Research Institute of Molecular Pathology (IMP), Vienna Biocenter (VBC), Campus-Vienna-Biocenter 1, Vienna, Austria. 2VRVis Research Center, Vienna, Austria. 3Bioinformatics and Scientific Computing, Vienna Biocenter (VBC), Vienna, Austria. 4Institute of Experimental and Clinical Pharmacology and Toxicology, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany. 5 Department of Zoology, University of Venda, Private Bag, Thohoyandou, Republic of South Africa

joanna.kaczanowska@imp.ac.at

Aims: Tracking evolutionary traces of human cognitive evolution in human phylogeny.

Methods: We fused evolutionary genomics with human functional neuroanatomy to reconstruct the neurogenetic evolution of human brain functions. To this end, we used genome-wide selection pressure (dN/dS ratios) in sets of chronologically ordered pairs of species (Pairwise Species Comparisons – PSCs) to trace patterns of selection in mammalian phylogeny linking mouse with human (see graphics below). As the method requires only the genomic data as input, we could include archaic genomes of extinct hominins (Neanderthal and Denisovan) in our analysis.

By mapping the genetic homologs, weighted by their dN/dS values, onto the human brain we generated an evolutionary atlas of human brain. Biclustering of highly selected genes in each PSC with human functional networks identified the top-selected brain networks in primate phylogeny.

Results: The temporo-spatial maps of cumulative neurogenetic selection reveal high selection pressure on subcortical brain regions (striatum, basal forebrain, brain stem) in early diversification periods (rodents-monkeys-apes). In the Hominid branch, the strongest selection concentrated on cortical, amygdalar and thalamic areas.

Biclustering of highly selected genes and brain networks from task-evoked functional MRI unmasked early emergence of resting state networks (DMN, salience, CEN), attention and sensorimotor networks in mammalian phylogeny. Interestingly, Hominids (chimp-archaic homo-humans), most strongly evolved networks for language, theory of mind, working memory and reward behaviors.

Conclusions: These data suggest accelerated neurogenetic selection for language and verbal communication across all hominin lineages. In addition, the predictions identified strategic thought and decision making as the dominant traits that may have separated modern humans from archaic hominins.

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ENDOGENOUS OLIGODENDROGLIAL ALPHA-SYNUCLEIN AND TPPP/P25A ORCHESTRATE ALPHA-SYNUCLEIN PATHOLOGY IN EXPERIMENTAL MULTIPLE SYSTEM ATROPHY MODELS

Panagiota Mavroeidi[1], Fedra Arvanitaki[1], AnastasiaKiriaki Karakitsou[1], Maria Vetsi[1], Ismini Kloukina[2], Markus Zweckstetter[3,4], Stefan Becker[4], Zachary A. Sorrentino[5,6], Benoit I. Giasson[5,6,7], Poul Henning Jensen[8], Leonidas Stefanis[1,9], Maria Xilouri[1]

1 Center of Clinical Research, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens (BRFAA), Athens, Greece;

2 Center of Basic Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece;

3German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany;

4Department for NMR-based Structural Biology, Max Planck Institute for Biophysical Chemistry, Göttingen, Germany;

5Department of Neuroscience, University of Florida, Gainesville, FL, United States;

6Center for Translational Research in Neurodegenerative Disease, University of Florida, Gainesville, FL, United States;

7McKnight Brain Institute, University of Florida, Gainesville, FL, USA;

8DANDRITE-Danish Research Institute of Translational Neuroscience and Department of Biomedicine, University of Aarhus, Aarhus C, Denmark;

9 1st Department of Neurology, Eginition Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

pmavroeidi@bioacademy.gr

Aim: Multiple system atrophy is characterized by the presence of distinctive glial cytoplasmic inclusions (GCIs) within oligodendrocytes that are mainly composed of the neuronal protein alpha-synuclein (aSyn) and the oligodendroglia-specific phosphoprotein TPPP/p25α. The aim of our study is to decipher the role of oligodendroglial aSyn and p25α in the formation of aSyn-rich GCIs.

Methods: We have applied human aSyn Pre-Formed Fibrils (PFFs) to the living brain of mice or to wild-type rat oligodendroglial cells and cells overexpressing human aSyn or p25α, as well as to primary differentiated oligodendrocytes derived from WT, aSyn-KO and PLP-haSyn-transgenic mice and studied the formation of pathological aSyn species by western blot and immunofluorescence.

Results: haSyn PFFs are readily uptaken by all oligodendroglial cells and recruit the endogenous oligodendroglial aSyn into the formation of pathological assemblies. Overexpression of human aSyn or p25α accelerates both the recruitment of the endogenous protein and the generation of aberrant aSyn species. In haSyn PFF-treated primary oligodendrocytes the microtubule and myelin networks are disrupted in a manner that is dependent upon the seeding of endogenous aSyn. Moreover, the pathology-related phosphorylation of aSyn at Ser129, depends on aSyn and p25α protein load and may involve different aSyn "strains" present in oligodendroglial and neuronal synucleinopathies. Finally, delivery of haSyn PFFs into the mouse brain leads to the formation of aberrant aSyn forms within oligodendroglia.

Conclusions: We propose that the endogenous aSyn and oligodendroglial phosphoprotein p25α form a dangerous dynamic duo that predisposes oligodendrocytes to accumulate aggregated aSyn into GCIs.

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MATERNAL DIET ALTERS THE HIPPOCAMPUS EPIGENETIC PATTERN IN PERINATAL ASPHYXIA

Sebastian Isac[1], Anca Maria Panaitescu[1,2], Amalia Udriste[3], Natalia Cucu[4], Gheorghe Peltecu[2], Leon Zagrean[1], Ana-Maria Zagrean[1]

[1] Division of Physiology and Neuroscience, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania.
[2] Filantropia Clinical Hospital, Bucharest, Romania.
[3] Research Center for Studies of Food Quality and Agricultural Products, Bucharest, Romania.
[4] Association for Epigenetics and Metabolomics, Bucharest, Romania

sebi_isac@yahoo.com

Perinatal asphyxia (PA) represents a major cause of neonatal morbidity with short and long-term neurological consequences. The aim of this study was to evaluate the influence of maternal dietary habits on the offspring's hippocampus epigenetic profile after PA.

The experimental groups were designed according to maternal diet: standard diet, trans-resveratrol enriched diet, citicoline supplemented diet or high-fat diet. Postnatal day 6 male Wistar rats, randomly selected from the dietary groups (n=8), were exposed for 90 minutes to a gas mixture of 9% O2, 20% CO2 and 71% N2, according to a previously described model of experimental PA.

Using qRT-PCR, we assessed 24 h after asphyxia exposure, the hippocampal expression of 5 non-coding microRNAs, miR124, miR132, miR134, miR146 and miR15a, known as epigenetic regulators involved in the neuronal development: synaptic plasticity, neuroinflammation, neuronal tolerance to asphyxia, memory formation and neuronal maturation.

The analysis was run twice. We expressed the miRNAs values relative to control by using double ΔCT method. Statistical significance was considered for a $p<0.05$.

Our results show that trans-resveratrol enriched maternal diet induces a significant hippocampal down-regulation of miR132 and miR15a in offspring exposed to PA . Moreover, citicoline supplemented maternal diet up-regulates miR124 and miR135 and down-regulates miR132 and miR15a . Finally, maternal high-fat diet induces a hippocampal up-regulation of miR124 and miR15a and a down-regulation of miR132.

In conclusion, our study proposes epigenetic markers as potential diagnostic and therapeutic tools that could be used in PA, a condition causing long-term deficits associated to mental and neurological diseases.

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GENERATING HUMAN SOMATOSTATIN RECEPTOR 4 (HSSTR4) EXPRESSING TRANGENIC MICE FOR PHARMACOLOGICAL RESEARCH

Balázs Nemes[1], Kata Bölcskei[1,2], Tímea Aczél [1,2], Adnan Ahmad Alkurdi[1], Yazan Abuawwad[1], András Dinnyés[3], Julianna Kobolák[3], Zoltán Sándor[1], Erika Pintér[1,2], Zsuzsanna Helyes [1,2]

[1]Department of Pharmacology and Pharmacotherapy, University of Pécs Medical School, Hungary.
[2]Centre for Neuroscience & Szentágothai Research Centre, University of Pécs, Hungary.
[3]BioTalentum Ltd, Gödöllő, Hungary

balazs.nemes@aok.pte.hu

Aims: We discovered that the somatostatin 4 receptor (sst4) mediates analgesic, anti-depressant and anti-inflammatory functions of somatostatin without endocrine actions. The aim of the present study is to design a humanized sst4 mouse model for preclinical testing of novel sst4 agonists.

Methods: We constructed a PiggyBac transposon vector containing human chromosomal fragment with the SSTR4 gene that also expresses the Luciferase-tdTomato reporter fusion protein. P2A self-cleaving site ensures that the human sst_4 is expressed separately from the reporter fusion protein not affecting the function.

We did transgenesis in SSTR4-deficient mice and one transgenic female was obtained which had offsprings. This first generation mother had several copies of the randomly inserted transgene. We bred mice carrying one copy of the transgene. With ligation-mediated PCR, we have located 3 copies on chromosome 3, 10 and X.

Results: In vivo imaging showed Luciferase luminescence in the brain with the strongest signal in the bulbus olfactorius, but tdTomato was not detectable either in vivo or on histological sections.In the elevated plus maze sst_4 KO mice spend less time on the open arms showing greater anxiety compared to wild types, but insertion of the human SSTR4 gene reversed this anxious phenotype providing evidence for its functionality.

Conclusion: The results are promising, the human transgenes are proved to be expressed, and the human receptor is showed to be functional. After further testing, this novel humanized model can be very useful for detecting pathology-related expression changes and the effect of our novel sst_4 agonists.

Acknowledgements for support:Richter Gedeon PhD scholarship KTIA_NAP_13-2-2014-0022 and KTIA_NAP_13-1-2013-0001 GINOP-2.3.2-15-2016-00050, EFOP-362-16-2017-00008207653/2018/FEKUTSTRAT

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P444

AMBROXOL INCREASES THE ENZYMATIC ACTIVITY GCASE IN PRIMARY MACROPHAGES DERIVED FROM PATIENTS WITH GBA-ASSOCIATED PARKINSON'S DISEASE

Kopytova A.E.[1], Nikolaev M.A.[1], Senkevich K.A.[1], Baydakova G.V.[2], Miliukhina I.V.[3], Zakharova E.Y.[2] , Pchelina S.N.[1]

1 Petersburg Nuclear Physics Institute named by B.P. Konstantinov of National Research Center «Kurchatov Institute», Saint-Petersburg, Russia;
2 Research Center for Medical Genetics, Moscow, Russia;
3 Institute of Experimental Medicine, Saint-Petersburg, Russia

kopytova_ae@pnpi.nrcki.ru

Mutations in the GBA gene lead to a deficiency of glucocerebrosidase (GCase) activity and to the development of Gaucher disease (GD). GBA mutations also increase the risk of Parkinson's disease (PD). Pharmacological chaperones could potentially enhance GCase activity and treat GD and PD linked to mutations in the GBA gene (GBA-PD).

Aims: The aim was to evaluate the effectiveness of the restoration of GCase activity in macrophages from GBA-PD patients using pharmacological chaperone ambroxol.

Methods: Mononuclear fraction was isolated from whole blood of GBA-PD patients (with mutations: N370S (n=3) and with L444P (n=3)) and healthy controls (n=4). With subsequent differentiation into macrophages using RPMI: 10% fetal bovine serum, 1% streptomycin-penicillin, 10 ng/ml M-CSF for 4 days. GCase activity and concertation of lysosphingolipids (hexosylsphingosine (HexSph)) were measured by LC-MS/MS in macrophage cells (2x10^6 cells/ml). Macrophages were treated with final concentration of ambroxol 50 μM.

Results: We showed an increase GCase activity in macrophages from GBA-PD patients with ambroxol 56,80 (29,35 – 115,14) mmol/l/h compared with cells without ambroxol 19,52 (8,30-27,67) ($p<0.001$). We also showed the decrease of HexSph concentration in macrophages from GBA-PD patients with ambroxol 31,68 (19,73 – 37,92) ng/ml compared with cells without ambroxol 48,26 (32,15 – 86,66) ng/ml ($p=0.015$).

Conclusions: Ambroxol increases GCase activity and decrease lysoscphingolipids concentration in primary macrophages from GBA-PD patients. We propose that ambroxol should be further investigated as a potential drug for PD treatment. Macrophage culture is suitable for screening of new potential GCase pharmacological chaperones.

The study was supported by RSF № 17-75-20159

P445

LONG-TERM TREATMENT WITH NAPROXEN DECREASES THE NUMBER OF SP-IMMUNOREACTIVE PORCINE DUODENAL NEURONS

Całka J, Czajkowska M

Department of Clinical Physiology, Faculty of Veterinary Medicine, University of Warmia and Mazury in Olsztyn, Poland

calkaj@uwm.edu.pl

Aim: Gastrointestinal inflammation resulting from prolonged NSAID drugs treatment constitutes a worldwide medical problem. Recently the role of enteric neuroactive substances involved in this process has gained attention. Therefore the aim of the study was to determine the effect of inflammation caused by naproxen supplementation on substance P (SP) expression in enteric duodenal neurons in domestic pigs.

Methods: Eight immature pigs of the Pietrain x Duroc race (20 kg of body weight) were used. Control animals (n=4) received empty gelatine capsules. Naproxen treated pigs (n=4) were given naproxen for 4 weeks, orally 50 mg/kg daily, approximately 1 h before feeding. Then animals from both groups were euthanized. Frozen sections were prepared from the collected material and subjected to double immunofluorescence staining. Primary antibodies against neuronal marker PGP 9.5 and SP were visualised with Alexa Fluor 488 and 546. Sections were analysed under Olympus BX51 fluorescence microscope.

Results: Microscopic analysis showed significant decrease in the number of SP positive neurons, both in the myenteric and submucous plexuses of the porcine duodenum.

Conclusions: Decreased number of the SP-immunoreactive neurons in the myenteric and submucous plexuses following naproxen evoked duodenal inflammation may reflect impairment of the local sensory transduction and/or down regulation of the inflammatory process.

This study was supported by the National Science Centre (grant no. 2018/29/N/NZ4/00348).

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THERAPEUTIC EFFECT OF RILUZOLE ON CAVERNOUS NERVE INJURY-INDUCED ERECTILE DYSFUNCTION

Elif Nur Barut[1], Seckin Engin[1], Yesim Kaya Yasar[1,2], F. Sena Sezen[1,2]

1Department of Pharmacology, Faculty of Pharmacy, 2Drug and Pharmaceutical Technology Application and Research Center, Karadeniz Technical University, Trabzon, Turkey

elifgazioglu@ktu.edu.tr

Aims: Neurogenic erectile dysfunction (ED) is a common complication of radical prostatectomy (RP) leading to significant decrease in quality of life. Neuroprotective treatment strategies for post-RP ED treatment have been of great interest since currently available drugs posses a limited efficacy. Riluzole (RIL), a neuroprotective agent, is approved for the symptomatic treatment of a denegenerative motor neuron disease, however its potential effect on neurogenic ED is not known. This study investigated the effects of RIL on a rat model of neurogenic ED-induced by bilateral cavernous nerve injury (BCNI).

Methods: Male rats (3-4 months old) underwent BCNI or sham injury. Rats were then divided into vehicle (V) or RIL (8mg/kg/day, ip) treatment groups for 7 or 15 days (n=5-7/group). Cavernous nerve electrical stimulation (1, 4, and 8 volts) induced erectile function (EF) was evaluated as maximum intracavernous pressure (mICP) and total ICP while continously monitoring mean arterial pressure (MAP).

Results: mICP/MAP and total ICP/MAP were lower BCNI-V groups compared with sham-V groups at 7 and 15 days post-injury ($p < 0.001$, $p < 0.05$). RIL treatment prevented the decrease in EF compared with V treatment at day 15 following BCNI ($p < 0.001$) although EF was not different in BCNI-RIL and BCNI-V groups at day 7 ($p>0.05$).

Conclusions: Preservation of EF following 15 days of RIL treatment indicates a potential therapeutic use of RIL in post RP-ED, and further research is necessary to understand its neuroprotective mechanisms in peripheral autonomic neurons.

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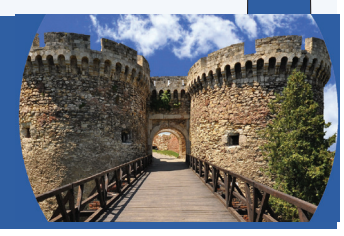

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P447

AGE AND SEX EFFECTS ON CORPUS CALLOSUM MORPHOLOGY: HUMAN AUTOPSY STUDY

Aysegul Gungor Aydin[1,2] , Esat Adiguzel[1,2], Kemalettin Acar[3]

1 Pamukkale University Faculty of Medicine Department of Anatomy, Denizli, Turkey. 2 Pamukkale University Institute of Health Sciences Neuroscience Department, Denizli, Turkey. 3 Pamukkale University Faculty of Medicine Department of Forensic Medicine, Denizli, Turkey

aysglgngr@gmail.com

Aim:Corpus callosum is the most significant part of the fiber groups form the interhemispheric connectivity between cortical neurons.Corpus callosum morphology may be affected by neurodegeneration/demyelination or vice versa.The white matter of telencephalon is essential for its functions.The corpus callosum morphology may provide information about the telencephalon physiology. We investigated the relationship between the midsagittal surface area of the corpus callosum and the effect of sex, age on this relationship in post mortem autopsy materials.

Methods:Total of 41 brains obtained from the forensic autopsy were included for study. The brain hemispheres were divided by midsagittally cutting after weighting.The corpus callosum was inspected and photographed at the interhemispheric aspect and photographs were transferred to the computer. SHTEREOM® software was used for measurement of the corpus callosum on the photographs.

Results:Mean area of the corpus callosum of female subjects(10.28±2.41) were lower than male subjects(12.11±2.72)(p=0.07). Males had larger areas in each region of the corpus callosum. The sex factor did not reach significance for the rostrum, corpus, and splenium. Also, for the genu, the male had a larger mean area than female (p=0.033). There was no significant correlation between age and corpus callosum area.However, a moderately significant negative correlation was found between corpus callosum area and age in 26 brains of individuals older than the age of 35(r=-0.390,p=0.003).In terms of the regions of the corpus callosum, a significant and negative correlation was found between the genu (r=-0.384,p=0.003),corpus (r=-0.336,p=0.011) regions and age.

Conclusion:These results are consistent with neuroimaging studies and contribute to insights into the diagnostic.

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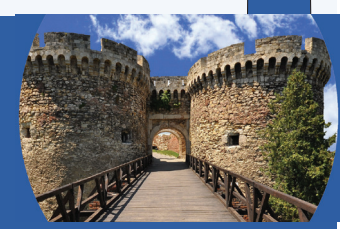

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UNCONVENTIONAL SECRETION OF MUTANT HUNTINGTIN

Katarina Trajkovic[1,2], Hyunkyung Jeong[1], Dimitri Krainc[1]

1Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, United States;
2Mediterranean Institute for Life Sciences (MedILS), Split, Croatia

katarina.trajkovic@medils.hr

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by the expansion of a CAG triplet in the gene encoding for huntingtin. The resulting mutant protein huntingtin (mHtt) with extended polyglutamine (polyQ) sequence at the N-terminus leads to neuronal degeneration both in cell-autonomous and non-cell-autonomous manners.

Recent studies identified mHtt in the extracellular environment and suggested that its spreading contributes to toxicity, but the mechanism of mHtt release from the cell of origin remains unknown. Therefore we performed a comprehensive, unbiased analysis of secretory pathways and identified an unconventional lysosomal pathway as an important mechanism for mHtt secretion in mouse neuroblastoma and striatal cell lines, as well as in primary neurons.

Moreover, we found that mutant huntingtin secretion can be significantly reduced by neutral sphingomyelinase and PI3-kinase inhibitors.

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CHOLINERGIC AGONISTS DEVELOP COMPLEX BURSTS IN DOPAMINERGIC NEURONS VIA NMDA RECEPTOR INDEPENDENT MECHANISM - IN VIVO ELECTROPHYSIOLOGICAL AND PHARMACOLOGICAL STUDIES ON NR1DATCREERT2 MICE

Magdalena Walczak[1], Łukasz Szumiec[2], Jan Rodriguez Parkitna[3], Tomasz Błasiak[1]

1Department of Neurophysiology and Chronobiology, Institute of Zoology and Biomedical Research, Jagiellonian University, Cracow, Poland;
2Department of Molecular Neuropharmacology, Institute of Pharmacology of the Polish Academy of Sciences, Cracow, Poland;
3Department of Molecular Neuropharmacology, Institute of Pharmacology of the Polish Academy of Sciences, Cracow, Poland

magda.kasia.walczak@gmail.com

Aims: Bursting mode of activity of dopaminergic neurons results in phasic increase of dopamine release whereas basal level of neurotransmitter is maintained by non-bursting firing of dopaminergic neurons. While functional NMDA receptors are considered to be crucial to evoke dopaminergic neurons' bursting activity, whether other neurotransmitters can also evoke bursts remains an opened question. Therefore, aim of our research was to determine effect of cholinergic agonists on activity of dopaminergic neurons lacking functional NMDA receptor.

Methods: We have used genetically modified strain of mice (NR1DATCreERT2) with deletion of NR1 subunit of NMDA receptor selectively on dopaminergic neurons of adult animals. We performed single unit, extracellular recordings of midbrain dopaminergic neurons' activity combined with iontophoretic application of cholinergic receptors agonists and antagonists in urethane anaesthetized mice.

Results: After application of non-selective cholinergic agonist carbachol, vast majority of dopaminergic neurons increased their firing rate. Interestingly, some of recorded cells, both in control and NR1DATCreERT2 mice developed slow, oscillatory changes in firing rate, which transformed into robust, complex bursts of action potentials. Neurons tested with oxotremorine application responded with an increase of firing rate and similarly to carbachol iontophoresis - some of the recorded neurons developed complex bursts.

Conclusions: These results show that activation of cholinergic receptors alone, without the involvement of NMDA receptors, can switch subpopulation of dopaminergic neurons into bursting mode of firing. Our studies suggest that muscarinic receptors can be involved in this phenomenon.

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NGF-INDUCED AUGMENTATION OF ADRENERGIC MODULATION OF CALCIUM CURRENTS IN CULTURED TRIGEMINAL GANGLION NEURONS

Mariia V. Telka, Oleg V. Ryhalsky, Nickolai S. Veselovsky

Bohomoletz Institute of Physiology, National Academy of Sciences of Ukraine, Kyiv, Ukraine

mariyka.t@gmail.com

Nerve growth factor (NGF) and adrenergic modulation of neuronal excitability play crucial role in sympathetically-maintained pain. The aim of present study was to characterize noradrenaline (NA) influence on trigeminal ganglion (TG) neurons excitability and to check the hypothesis that NGF could alter adrenergic modulation of Ca^{2+}-current.

Using whole cell recording technique, it was shown that TG neurons with different firing properties had different sensitivity to NA. In NA-sensitive TG neurons NA application (10-100μM) induced changes in their electrophysiological properties, particularly AP fall time and amplitude were reduced.

NGF influence on the adrenergic modulation was demonstrated as changes in characteristics of voltage activated Ca^{2+} currents (VACC) in TG neurons treated with NGF (100 ng/ml, 4 days). NA had no effect on low threshold VACC but inhibited high threshold VACC (hVACC). NA application resulted in decrease of hVACC maximum amplitude by (33±3) % and (12±2) % in NGF-treated and not-treated TG neurons respectively. In 11 out of 13 (85%) NGF-treated TG neurons NA depressed fast component of hVACC. Application of yohimbine (selective antagonist of $alpha_2$-adrenoceptors) abolished NA inhibition.

Our results demonstrate that high threshold voltage-activated Ca^{2+} channels are involved in NA modulation of TG neurons excitability. The data obtained suggest that NGF may cause an amplification of adrenergic modulation of Ca^{2+} current in TG neurons.

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NEURON-DEPENDENT ACTIONS OF FRACTALKINE IN THE RAT BASOLATERAL AMYGDALA. FOCUS ON EXCITATORY SYNAPTIC TRANSMISSION.

JE Sowa, G Hess, K Tokarski

Department of Physiology, Maj Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland

joannasowa91@gmail.com

Chemokines, together with neurotransmitters and hormones, are signaling molecules playing a key role in the maintenance of neuro-immune-endocrine system homeostasis. Yet, recognition and characterization of chemokines' effects on neurophysiology are still lacking. One of their member, fractalkine (CX3CL1), is a critical mediator in neuron-microglia crosstalk. It is mostly expressed in neurons, whereas its cognate receptor, CX3CR1, is mainly expressed in microglia. They are constitutively and diffusively expressed in the brain, however a high density of CX3CR1 is reported in structures such as hippocampus and amygdala. The amygdala is a crucial structure for integrating stress signaling as well as inflammatory responses from the periphery.

Therefore, this study aimed to elucidate the role of fractalkine in the rat basolateral amygdala (BLA), which may provide a deeper understanding of information processing and its possible role in mediating mood-related changes that occur in this area.

Whole-cell patch clamp recordings were performed using acute brain slices (300µm) containing the BLA. After recording a baseline in principal cells, fractalkine (2nM and 5nM) was bath-applied. Both inhibitory and excitatory synaptic transmission were measured by recording spontaneous (sIPSC/sEPSC) and miniature (mIPSC/mEPSC) synaptic currents. Specificity of observed effects was investigated using the same experimental protocol with additional incubation in a CX3CR1 antibody or minocycline (inhibitor of microglia activation).

Our data indicate that CX3CL1 increased the frequency of spontaneous EPSC as well as miniature EPSC in the CX3CR1-dependent action. This suggests a presynaptic, action potential-independent mechanism of CX3CR1 receptor activation. Interestingly, incubation in minocycline, which prevent microglia activation, did not abolish this effect, indicating that microglia was not involved in this phenomenon.

In conclusion, our data show that fractalkine has a profound effect on BLA synaptic activity, indicating that this protein can be an active modulator of neuronal activity in the fear-related response circuitry, which may have significant scientific and therapeutic implications.

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IN VIVO EFFECT OF *MACROVIPERA LEBETINA OBTUSA(MLO)* AND *MONTIVIPERA RADDEI (MR)* SNAKE VENOMS ON RATS NEUROMUSCULAR JUNCTION (*NMJ*)

[1]Kishmiryan AV, [2]Terzyan DO, [1]Ghulikyan LA, [1]Ghukasyan GV, [1]Meltonyan AV, [2]Manvelyan LR, [1]Ayvazyan NM

[1]Laboratory of Toxicology and Molecular Systematics, [2]Laboratory of Central Nervous System Physiology L. A. Orbeli Institute of Physiology NAS RA, Yerevan, Armenia

akishmiryan@gmail.com, dianaart@mail.ru

According to literature data venoms of some vipers besides hemorrhagic effect have also neurotoxic properties. Proceeding from the results of our previous in vitro study data the following investigations were implemented:

Neurotoxic effect at different periods of these venoms on *musculus soleus* of the rats was studied *in vivo* by the Electrophysiological Recordings method. *MLO* and *MR* venoms was diluted with physiological saline (0.9% NaCl, 1mg/ml and 1mg/2ml) to a final concentration of 240 µg/injection and 120 µg/injection respectively. Electrophysiological recordings of musculus soleus of rates injected with physiological saline was used as control group. Samples under study were divided into 3 groups according to the time passed after injection: 1) electrophysiological recording of musculus soleus were measured during 1 hour period, 30 minutes after injection 2) 24 hours after injection 3) 48 hours after injection. Single excitation of *musculus soleus* generates chemically initiated action potentials.

Latency of registered action potentials in the control group were ranging from 0.46 to 2 msec, the amplitude of the action potentials were ranging from 10 to 80 mV. The amplitude of the action potentials during 1 hour 30 minutes after injection of venoms of *MLO* and *MR* were decreased up to 0-15mV (total n=41) and 0-8mV (total n=48) respectively. There were no significant change in the remaining electrophysiological recordings. The latency period after 24 hour of injection of venoms of *MLO* were ranging from from 0 to 5.18 msec (total n=32), in the case of *MR* venoms, there were not detected any siginificant change (total n=30). The amplitude after 24 hour of injection were increased in cases of both venoms with significantly more increase with *MR* (*MLO* total n=32, *MR* total n=30). 48 hours after injection the registered latency period was little bit decreased compared to that in 24 hour after injection and the amplitude recovery of the amplitude up to 92 mV (*MLO* total n=34), in the case of *MR* venom, the latency period were not significantly changed reaching up to 3.47 msec, the amplitude were recovered up to 80mV (total n=32).

Hereby comparing the in vivo effects of this two types of venoms on NMJ electrophysiological parameters we can conclude that in both cases partial neuromuscular blockage occure durig 1 hour 30 minutes after venom injection which is recovered to some extenet after 24 hours (with more recovery with *MR* venom). 48 hours after injection of venoms the recovery of electrophysiological parameters of NMJ is continued in both cases.

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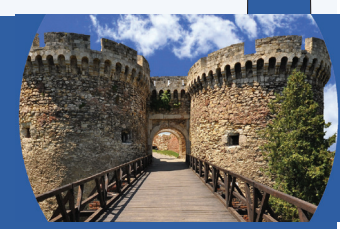

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DYNAMIC CHANGES OF AT2 RECEPTOR EXPRESSION AFTER TRAUMATIC SPINAL CORD INJURY

Fedorova J., Demkovicova E., Mucha R., Pavel J.

Institute of Neurobiology, Biomedical Research Center, Slovak Academy of Sciences, Kosice, Slovakia

jfedorova@saske.sk

The renin-angiotensin system (RAS) through its main effector neuropeptide Angiotensin II is widely known for regulation of blood pressure and fluid homeostasis. The most biological effects of Angiotensin II are mediated via AT1 receptor but in the last two decades it became clear that RAS is much more complex and signaling transduction via AT2 receptor (AT2R) plays also an important role. The AT2 R under normal conditions is only sparsely expressed in the most tissues. However, it is strongly upregulated following tissue damage including neuronal injury. Recent studies indicated that the selective stimulation of AT2R has a great therapeutic potential for extremely serious injuries like brain traumatic injury, peripheral nerve injury, stroke and spinal cord injury. The beneficial effect of such stimulation depends on its appropriate timing. Therefore, the regional distribution of AT2R after 40g spinal cord compression lasting 15 minutes at the Th9 level during 28-days survival period was studied in our experiments. Our results determined by Angiotensin receptor binding, RT-PCR and WB analyses showed that the level of AT2R in lesion epicenter is slightly increased, however, it is significantly upregulated in adjacent regions in cranio-caudal direction from it. The evaluation of AT2R expression in trauma-injured spinal cord at the different time points (1-3-7-14-21-28 days) revealed a marked dynamic changes that are region- as well as time-dependent.

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THE KAINATE RECEPTOR SUBUNIT GLUK2 INTERACTS WITH KCC2 TO PROMOTE DENDRITIC SPINE FORMATION

Kesaf Sebnem[2,1], Khirug Stanislav[1], Dinh Emilie[3], Garcia Saez Marta[1], Taira Tomi[4], Lauri Sari[2], Rivera Baeza Claudio[1,5]

1HiLIFE Neuroscience Center, University of Helsinki, Helsinki, Finland;
2Molecular and Integrative Biosciences Research Program, University of Helsinki, Helsinki, Finland;
3Developmental Biology Institute of Marseille, Marseille, France;
4Veterinary Biosciences, University of Helsinki, Helsinki, Finland;
5Institut de Neurobiologie de la Méditerranée INMED UMR901, Marseille, France

sebnem.kesaf@helsinki.fi

The interplay between glutamatergic and GABAergic transmission is crucial for the synaptic maturation during development. Impairments in the balance of neurotransmission may result in various neurodevelopmental disorders, which are associated with the abnormal regulation of dendritic spines. The morphology of dendritic spines is regulated by the remodeling of actin cytoskeleton with a complex network of signaling molecules. Previous results have shown that K- Cl cotransporter, KCC2, has a morphogenic role in maturation of dendritic spines via the structural interaction with spectrin-actin binding protein 4.1N. In addition, GluK2 kainate receptor subunit was shown to coexist in a functional complex with KCC2 to regulate its function and surface expression. In this study, we focused on the role of the GluK2-KCC2 interaction for the regulation of dendritic spine development. We found that the shRNA-mediated knockdown of GluK2 did not differ the density of total dendritic spines compared to controls in vivo, however the density and percentage of thin spines significantly increased, which is the reminiscence of immature state of neuron. Consistent with this, the neurons infected with shRNA GluK2 displayed a lower frequency of mEPSC. In CA3 region of hippocampus, KCC2 showed a strong perisomatic pattern of immunoreactivity in controls, whereas a cytoplasmic pattern of immunoreactivity in shRNA GluK2 infected neurons. CA3 pyramidal neurons infected with shRNA GluK2 resulted in a smaller somato-dendritic gradient, reflecting the efficacy of KCC2 function as well as its decreased surface expression. In cultured rat hippocampal neurons, shRNA-mediated knockdown of GluK2 significantly reduced the density of dendritic spines and this effect was rescued by the overexpression of KCC2. At last, we studied the effect of GluK2 knockdown on actin dynamics using fluorescence recovery after photobleaching (FRAP). FRAP data has shown the increased stability of F-actin filaments of dendritic spines in hippocampal cultures after GluK2 knockdown as a result of increased phosphorylation ratio of actin depolymerizating factor cofilin. In conclusion, our results demonstrate that GluK2-KCC2 interaction developmentally regulates dendritic spine formation and its stability.

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SIGNIFICANT CHANGES OF PLASMA N-GLYCOME IN PATIENTS WITH PTSD

Lucija Tudor[1], Matea Nikolac Perkovic[1], Gordana Nedic Erjavec[1], Dubravka Svob Strac[1], Marcela Konjevod[1], Suzana Uzun[2], Oliver Kozumplik[2], Nela Pivac[1]

1Division of Molecular Medicine, Rudjer Boskovic Institute, Zagreb, Croatia;
2Clinic for Psychiatry Vrapce, Zagreb, Croatia

lucija.tudor@gmail.com

Introduction: Posttraumatic stress disorder (PTSD) is trauma-related disorder that represents heavy socio-economic burden due to its complex and still unknown etiology, lack of validated biomarkers, and numerous comorbidities. Protein glycosylation affects majority of proteins present in blood plasma and can introduce changes in protein function and selectivity, therefore resulting in alternate cell signalling and possibly contributing to pathogenesis of different diseases as well as premature aging.

Aim: The aim of this study was to examine N-glycome differences in blood plasma of PTSD and control subjects and to replicate the results in an independent cohort.

Methods: All participants were unrelated males of Croatian origin. Plasma glycosylation was determined using ultra-high performance liquid chromatography resulting in 39 N-glycan peaks. The difference in N-glycan distribution between PTSD subjects and controls were evaluated with Mann-Whitney test and was corrected for the effect of age and multiple testing.

Results: Out of 19 altered N-glycans in the first cohort, 6 N-glycans were replicated in both cohorts: 4 N-glycan were significantly higher, and 2 N-glycan were significantly lower in PTSD subjects compared to controls. These glycans were also following the same pattern of distribution in inflammatory processes and in older age.

Conclusion: N-glycome of the individual is considered an adaptive answer to the environment. Specific changes of N-glycans in patients with PTSD, which were also observed in different pathophysiological states, suggest the role of N-glycans in PTSD pathogenesis.

This research was supported by the Croatian Science Foundation, project No. IP-2014-09-4289.

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P456

THE ROLE OF LIPOCALIN 2 IN THE REGULATION OF BRAIN DEVELOPMENT

Martyna Pekala, Leszek Kaczmarek, Katarzyna Kalita
Nencki Institute of Experimental Biology, Warsaw, Poland

m.pekala@nencki.gov.pl

Aims: Epidemiological studies indicate that maternal infection during pregnancy is a risk factor for neurodevelopmental disorders. However, the mechanisms underlying this phenomenon remains unclear. One of the highly expressed proteins in the adult brain in response to infection is Lipocalin 2 (Lcn2), an innate immune response protein. The aim of our studies is to characterize the role of Lcn2 in the regulation of neuronal circuitry development.

Methods: To mimic maternal infection the pregnant mice received three *i.p.* injections of lipopolysaccharide or PBS on E15, 16, and 17, representing infection in the second-trimester pregnancy in humans. To evaluate Lcn2 mRNA and protein expression in the fetal brain we performed qRT-PCR and immunohistochemical staining on brain tissue isolated 24 hours after the last injection. Also, we quantified Lcn2 expression in the hippocampus during postnatal development. To address how lack of Lcn2 can affect the function of the adult brain we performed electrophysiological recordings on Lcn2 KO and WT animals after acute exposure to LPS.

Results and conclusions: Lcn2 mRNA is developmentally regulated in the hippocampus *in vivo,* with the highest expression between P0 to P21. Moreover, Lcn2 is significantly upregulated in the brain in response to prenatal infection. In the adult brain, we observed that the lack of Lcn2 causes higher neuronal excitability after acute infection. These results suggest that Lipocalin 2 could be a promising link between immune response and brain development, however to answer questions regarding its role in neurodevelopmental disorders more studies are required.

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P457

IMPAIRMENT OF CHAPERONE-MEDIATED AUTOPHAGY IN RATS IS ACCOMPANIED BY ABERRANT INDUCTION OF MACROAUTOPHAGY IN THE DEGENERATING NIGROSTRIATAL AXONAL TERMINALS

Fouka M.[1], Kloukina I.[2], Xilouri M.[1] and Stefanis L.[1,3]

1Center of Clinical Research, Experimental Surgery and Translational Research,Biomedical Research Foundation of the Academy of Athens, Greece;
2Center of Basic Research, Biomedical Research Foundation of the Academy of Athens, Greece;
3First Department of Neurology, Hospital Eginition, University of Athens, Medical School, Greece

maria_fouka@hotmail.com

Aims: Aim of the current study was to assess the contribution of macroautophagy to the dopaminergic axonal degeneration that precedes nigral cell death, evoked by inhibition of the Chaperone-mediated autophagy (CMA) pathway.

Methods: In order to inhibit CMA, we have stereotaxically injected adeno-associated viruses expressing shRNAs targeting LAMP2A receptor or scrambled shRNAs in the rat substantia nigra (SN). At 2 and 3 weeks post-injection, we examined indices of macroautophagy induction and the formation of autophagic vacuoles (AVs) in the nigrostriatal axis by Confocal and Electron Microscopy. The integrity of the nigrostriatal projections and the astro- and micro-gliosis in both striatum and SN at these time-points were also assessed by Confocal Microcscopy.

Results: LAMP2A down-regulation was accompanied by abnormal accumulation of AVs at synaptic nerve terminals, prior to dopaminergic degeneration at 3 weeks post-injection. At this early time point, the levels of Bassoon, a negative regulator of autophagy and a marker for the active synaptic zone, were decreased, whereas levels of ULK-1 were increased. Increased astro- and micro-gliosis was observed in both SN and striatum.

Conclusion: Our data suggest that uncontrolled induction of macroautophagy may, at least in part, be responsible for the nigrostriatal terminal degeneration that occurs early in this model, well before cell soma degeneration. Further, our results provide the first *in vivo* evidence that ULK-1 is a CMA substrate and may act as a link between CMA and macroautophagy. Therefore, down-regulation of macroautophagy may represent a promising target to reverse the damage and rescue the deteriorating dopaminergic neurons.

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P458

MFN2 LOSS AFFECTS NEURONAL FUNCTION AND MORPHOLOGY IN HIGH-ANXIOUS RATS

Elias Gebara[1,2], Simone Astori[1,2], Bernard Schneider[2], and Carmen Sandi[1,2]

[1]Laboratory of Behavioral Genetics, [2]Brain Mind Institute, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

elias.gebara@epfl.ch

Mitochondrial dysfunction is increasingly implicated in brain function and psychopathologies. Mitofusin 2 (Mfn2) is molecule involved in mitochondrial dynamics and is essential for the regulation of energy production under stress conditions and for mitigating mitochondrial resulting from environmental challenges. In this study, we investigate the involvement of Mfn2 in a brain region, the nucleus accumbens that plays a key role in motivation and is implicated in depression, in the vulnerability to develop anxiety and depression following stress exposure. Wistar outbred rats were first classified as high- or low-anxious based on natural variation for anxiety-like behavior on the elevated plus maze. High-Anxious rat displayed a decrease in Mfn2 RNA and protein levels, coupled with a change mitochondria morphology and function. These changes results in an alteration in neuronal morphology and physiology affecting the behavior. We injected a Mfn2 overexpressing AAV in the nucleus accumbens of high-Anxious rat and we found that after 4 weeks of incubation we restore the neuronal morphology and the behavior. Our results suggests that mfn2 plays a major role in the neuronal function and the anxiety related behavior.

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P459

SUBSTANTIAL CHANGES IN MACROGLIAL CELL MORPHOLOGY, DENSITY AND ACTIVATION AFTER EPIDURAL IMPLANTATION OF A SMALL ELECTRIC STIMULATOR IN RATS WITH SPINAL TRAUMA

Bacova, M., Bimbova K., Lukacova, N., Galik, J.

Institute of Neurobiology of Biomedical Research Center of Slovak Academy of Sciences, Kosice, Slovak Republic

bacova@saske.sk

Reactive astrogliosis is a pathological hallmark of spinal cord injury (SCI) characterized by profound morphological, molecular and functional changes in astrocytes after SCI. Astrocytic scar, the final form of reactive astrogliosis, is widely regarded as a principal cause of axonal re-growth failure and poor functional outcome. In our study, SCI was performed by the compression device at the Th9 level. The miniature oscillating field (OF) stimulator with electrodes placed over the injury site was implanted in order to promote subsequent regeneration. The Wistar rats were used and divided into 3-groups: a) untreated group (SCI) - animals with spinal cord injury; b) treated group (OFS+SCI) - SCI animals with OF stimulator; c) control group (nOFS+SCI) - SCI animals with non-functional OF stimulator. After 4 weeks of survival, the animals were transcardially perfused, and the spinal cord segments (Th7-Th11) were used for immunohistological and histological analysis. Our results show strong differences in activated astrocytes count and density in treated, untreated and control group. The number of activated astrocytes in the dorsal and lateral columns was significantly lower in the OFS+SCI group compared to the SCI and nOFS+SCI group. In addition, densitometric analysis confirmed that implantation of OF stimulator has beneficial role in reducing astrogliosis, and GFAP (typical for astrocytes) immunoreactivity was strongly decreased in the animals treated with OF stimulation compared to the SCI and control group.

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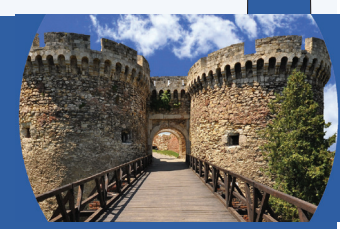

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P560

ENDURANCE TRAINING APPLIED BEFORE SPINAL CORD INJURY PROMOTED THE EXPRESSION OF GROWTH FACTORS AND THEIR RECEPTORS AT LESION SITE

Bimbova K, Bacova M, Stropkovska A, Kisucka A, Lukacova N

Institute of Neurobiology of Biomedical Research Center of Slovak Academy of Sciences, Kosice, Slovak Republic

bimbova@saske.sk

The aim of our study was to determine whether endurance training applied before spinal cord injury (SCI) affects the mRNA-expression of growth factors (BDNF, GDNF) and their receptors (TrkB, Gfr-alpha1) in cervical (C1-C8), thoracic (Th7-Th11) and lumbar (L1-L6) segments. Wistar rats were divided into 4 experimental groups: 1) control; 2) Six-weeks lasting endurance training (the intensity of training was gradually increasing from 27 cm/s to 46.6 cm/s); 3) Th9-compression; 4) Training + SCI. The animals after SCI survived 6-weeks. In control, the expression of growth factors and their receptors was significantly higher in cervical and lumbar segments than in thoracic segments. Endurance training, SCI or endurance training + SCI did not affect the expression of *BDNF, GDNF, TrkB or* Gfr-alpha1 at cervical and lumbar level. The levels of mRNAs in these segments remained approximately constant in each group. Marked differences in the levels of mRNAs were detected in thoracic segments. The expression of growth factors and their receptors in control was as follows: BDNF (4.3±0.15), GDNF (5.72±0.6), TrkB (2.2±0.25) and Gfr-alpha1 (2.23±0.49). Endurance training significantly (up to 3-times) increased the expression of growth factors, when compared to control. Endogenous stimulation of growth factors promoted the functional plasticity and neuronal growth after SCI. In group of trained animals+SCI the gene expression was 2-fold higher than in the non-trained SCI-group. The results show, that BDNF, GDNF and their receptors- TrkB and Gfr-alpha1 are strongly modulated by endurance exercise at thoracic level.

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P461

DYSREGULATION OF AUTOPHAGY AND STRESS GRANULE-RELATED PROTEINS IN STRESS-DRIVEN TAU PATHOLOGY

Joana Margarida Silva[1,2], Sara Rodrigues[1,2], Akihiko Takashima[3], Benjamin Wolozin[4], Nuno Sousa[1,2], Ioannis Sotiropoulos[1,2]

1 Life and Health Sciences Research Institute (ICVS), Medical School, University of Minho, Campus Gualtar, Braga, Portugal;
2 ICVS/3B's - PT Government Associate Laboratory, Braga/Guimarães, Portugal;
3 Department of Life Science, Faculty of Science, Gakushuin University, Tokyo, Japan;
4 Department of Pharmacology & Experimental Therapeutics, School of Medicine, Boston University, MA, Boston, United States

joanamsilva@med.uminho.pt

Aim:Imbalance of neuronal proteostasis associated with misfolding and aggregation of Tau protein is a common neurodegenerative feature in Alzheimer' s disease (AD) and other Tauopathies. Consistent with suggestions that lifetime stress may be an important AD precipitating factor, we previously reported that environmental stress and high glucocorticoid (GC) levels induce accumulation of aggregated Tau; however, the molecular mechanisms for such process remain unclear. Herein, we monitor a novel interplay between RNA-binding proteins (RBPs) and autophagic machinery in the underlying mechanisms through which chronic stress and high GC levels impact on Tau proteostasis precipitating Tau aggregation.

Methods & Results: Using molecular, pharmacological and behavioral analysis, we demonstrate that chronic stress and high GC trigger mTORdependent inhibition of autophagy, leading to accumulation of Tau aggregates and cell death in P301L-Tau expressing mice and cells. In parallel, we found that environmental stress and GC disturb cellular homeostasis and trigger the insoluble accumulation of different RBPs, such as PABP, G3BP1, TIA-1, and FUS, shown to form stress granules (SGs) and Tau aggregation. Interestingly, an mTOR-driven pharmacological stimulation of autophagy attenuates the GC-driven accumulation of Tau and SG-related proteins as well as the related cell death, suggesting a critical interface between autophagy and the response of the SG-related protein in the neurodegenerative potential of chronic stress and GC.

Conclusion: These studies provide novel insights into the RNA– protein intracellular signaling regulating the precipitating role of environmental stress and GC on Tau-driven brain pathology.

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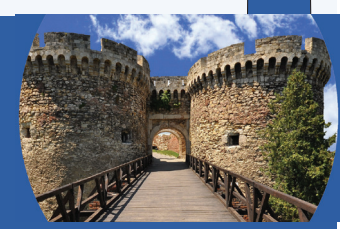

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P462

ROLE OF THE GLUTAMATE IN REMOTE ISCHEMIC TOLERANCE INDUCED BEFORE GLOBAL CEREBRAL ISCHEMIA

Jachová, J., Gottlieb, M., Némethová, M., Mačáková, L., Bonová, P.

Institute of Neurobiology, Slovak Academy of Sciences, Kosice, Slovak republic

jachovaj@gmail.com

Ischemic tolerance is endogenous neuroprotective mechanism, that could be induced by application of various types of sublethal stress, remote organ ischemia including. Extracellular elevation of glutamate is one of the first events in ischemia affected brain tissue. Its increased concentration after stroke was recorded also in circulating blood. Because of its important role in ischemic injury mechanism, we decided to study its potential role in ischemic tolerance induction.

We focused on the changes of glutamate concentration in nerve tissue and in blood after global brain ischemia with and without early (1 hour) remote preconditioning during seven days of reperfusion. Impact of ictus was valorised by determination of degenerated neurons by Fluorojade B staining.

Our results showed that pretreatment of animals with hind limb ischemia maintained tissue

glutamate level in the rage of control compare to ischemic group, where we observed significant elevation after one day of reperfusion. In contrast to this, its blood level raised over the control and during the first four days was significantly elevated compare to ischemia group. Neuroprotective effect of preconditioning was confirmed by decreased number of degenerating neurons by 44 %.

Based on our results, glutamate seems to be important not only in ischemia but also in ischemic tolerance induction. Because increased level of glutamate in circulating blood of preconditioned animals was observed, we can assume, that elevated brain to blood glutamate efflux would represents one of the neuroprotective mechanism induced by ischemic tolerance.

This study was supported by grants *No. VEGA 2/0094/18 a VEGA 2/0029/18.*

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P463

BREAKDOWN OF THE AFFECTIVE-COGNITIVE NETWORK IN FUNCTIONAL DYSTONIA

Aleksandra Tomić[1],*, Igor Petrović [1], Marina Svetel[1], Nataša Dragašaević Mišković[1], Elisa Canu[2], Federica Agosta[2], Elisabetta Sarasso[2], Noemi Piramide[2], Alberto Inuggi[4], Massimo Filippi[2,3], Vladimir S. Kostic[1]

1Clinic of Neurology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia;
2Neuroimaging Research Unit, and 3Department of Neurology, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy;
4Unit of Robotics, Brain and Cognitive Sciences, Istituto Italiano di Tecnologia, Genoa, Italy

alexandra_tomic@yahoo.co.uk

The role of the affective-cognitive network was explored in two clinical phenotypes of functional dystonia (FD): fixed (FixFD) and mobile dystonia (MobFD). Resting state fMRI was obtained from 40 FD patients (12 FixFD; 28 MobFD) and 43 controls (14 young FixFD-age-matched [yHC]; 29 old MobFD-age-matched [oHC]). Functional connectivity (FC) of the ventromedial prefrontal cortex (vmPFC), right temporoparietal junction (rTPJ), dorsal anterior cingulate cortex (dACC), bilateral medial dorsal nucleus (MDN) of thalamus and affective-cognitive part of cerebellum (AC-cerebellum) was assessed.

Compared to HC, both FD patient groups showed enhanced FC between the right AC-cerebellum and the bilateral associative parietal cortex, with greater enhancement in FixFD cases. Compared to oHC, MobFD showed reduced FC between vmPFC, left MDN and the bilateral anterior PFC; and enhanced FC between bilateral MDN and the bilateral associative parietal and visual cortices. Compared to yHC, FixFD showed reduced FC between vmPFC, right MDN, rTPJ, dACC and bilateral PFC and premotor cortex, and between dACC and right primary motor cortex and insula. Compared to MobFD, FixFD patients showed enhanced FC between dACC, left MDN and rTPJ and bilateral primary, premotor, associative and limbic structures. The two FD phenotypes showed similar altered affective-cognitive network connectivity in PFC reflecting patient difficulties in cognitive control and motor inhibition. Sensorimotor connectivity was more disrupted in the FixFD group, with unique involvement of dACC and rTPJ, which are crucial regions for emotion regulation, awareness and sense of agency.

These findings suggest that brain functional connections may modulate the phenotypic expression of FD.

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Brain Awareness Week Posters

BAW1

BRAIN AWARENESS WEEK 2019 – SCIENCE VS ART IN THE AGE OF ARTIFICIAL INTELLIGENCE

Robert Mihai Haret[1], Patricia Demetria Popovici[1], Miruna Rascu[1], Mihai Stancu[1], Raluca Mitran[1], Marina Cozma[1], Miruna Rascu[1], Catalina Sabina Cremeneanu[1], Miralena Tomescu[2], Alexandru Catalin Paslaru[3], Ana-Maria Zagrean[3] and Mihai Moldovan[3]

[1]Scientific Organization of Medical Students, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [2]Laboratory of Cognitive Development and Applied Psychology through Immersive Experiences, Bucharest, Romania, [3]National Neuroscience Society of Romania & Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

robert.haret@stud.umfcd.ro

For the 2019 edition of Brain Awareness Week, the National Neuroscience Society of Romania and the Scientific Organization of Medical Students partnered up with the Laboratory of Cognitive Development and Applied Psychology through Immersive Experiences (LDCAPEI, CINETic). Our events took place at Carol Davila University of Medicine and Pharmacy and CINETic lab and focused on the topics of perception of reality and tech solutions used for sensory augmentation. We organized a vast array of activities comprising of interactive presentations, workshops, a satellite conference and multiple open lab days. BAW2019 began with a conference where Alexandru Berceanu, Bogdan Mustata, and Dragos Cinerci, researchers and artists from CINETic, presented and argued the connection between science and art. The Neuroscience Laboratory at Carol Davila University of Medicine and Pharmacy hosted events where we focused on explaining different laboratory techniques used in neuroscience research, thus introducing the participants in the laboratory environment. At CINETic, participants experienced one of the ongoing VR projects on sensory experience in immersive virtual reality. Coming from a medical school, BAW could not lack a special neurology edition of our regular event, TIPS (Training with Interactive Presentations for Students), an entertaining workshop for students with the aim of learning and practicing clinical thinking. The final day brought us the interactive lecture conducted by Professor Leon Zagrean at Carol Davila University of Medicine and Pharmacy. The BAW events were a great success, raising the interest of many curious people, initiating brainstorming discussions accessible for people from all walks of life: medical students, artists, bioengineers, IT scientists and general public.

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Brain Awareness Week Posters

BAW2

BRAIN AWARENESS WEEK 2018 – BRAIN TECHNOLOGY: THE QUEST FOR HUMAN ENHANCEMENT

Mihai Stancu[1], Patricia Demetria Popovici[1], Robert Mihai Haret[1], Raluca Mitran[1], Miruna Rascu[1], Vlad Petru Morozan[1], Ana-Maria Zagrean[2], Alexandru Catalin Paslaru[2] and Mihai Moldovan[2]

[1]Scientific Organization of Medical Students, [2]National Neuroscience Society of Romania, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

mail.stancu.mihai@gmail.com

As long-term partners in neuroscience outreach, the National Neuroscience Society of Romania and the Scientific Organization of Medical Students organized a series of events for the 2018 Brain Awareness Week at Carol Davila University of Medicine and Pharmacy in Bucharest, Romania, on the topic of "Brain Technology – The quest for human enhancement". We organized a variety of events, ranging from a FameLab competition, where students were encouraged to engage in effective science communication related to Brain Technology, to a visit in the Neuroscience Laboratory at our faculty. Here, different techniques and experiments were presented, the main attraction being a demo in which people had their own EEG recorded while immersed in virtual reality. Coming from a medical school, BAW could not lack a special neurology edition of our regular event, TIPS (Training with Interactive Presentations for Students), an entertaining workshop for students with the aim of learning and practicing clinical thinking. The last two days belonged to the Keynote conferences, held by Professor Leon Zagrean, from our university, and his guests, Ioan Opris from University of Miami, and Marius Leordeanu and Catalin Dumitrescu from Politehnica University Bucharest. They approached exciting topics such as the relationship between vision and language, the possibility of memory prostheses and recent technological advancements in a diverse array of fields. Our topic raised the interest of many curious people, making it accessible for a variety of people from all walks of life: medical students, artists, bioengineers, IT scientists, general public etc. Our BAW2019 were generously awarded by The Dana Foundation/EDAB and FENS.

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Brain Awareness Week Posters

BAW3

THE LIFE OF BRAIN

Ankica Janković, Magdalena Biočanin, Jovana Babić, Anđela Đinovski, Emilija Romić

Student Section of the Serbian Neuroscience Society, Belgrade, Serbia

ankicajankovic3@gmail.com

During March 2019, for the 8th time in Belgrade, Student Section of the Serbian Neuroscience Society was included in celebration of popular manifestation Brain Awareness Week. As every year, various activities were prepared in aim to promote knowledge about brain in a simple and creative way for wide audience. The theme was "The Life of Brain" in which we covered some of the most interesting topics in the field of neuroscience. Through interactive exhibition we tried to tell the story of brain development, epigenetics, interdependence between brain and gut as well as developmental and neurodegenerative disorders. Visitors could also experience certain topics in an unusual and intriguing way, learn about brain structure and communication of neurons through models of electrical and chemical synapses. The youngest science lovers were part of the manifestation in educative and creative workshop named ``Starry sky`` where they painted the neurons and could find out what is that special thing called brain. Workshop about depression was prepared for highschool students where we wanted to speak about serious and contemporary problem and emphasize the importance of taking care of mental hygiene. Faculties and institutes involved in any aspect of nervous system research organized ``Laboratory open days`` to make opportunity for interested students to meet scientists and see what they do in their laboratories. Also, lectures on brain-related topics were held everyday by some of the most appreciated experts and scientists. During the BAW volonteers had good time while sharing love and enthusiasm for neurosciences.

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Brain Awareness Week Posters

BAW4

STUDENT SECTION OF THE SERBIAN NEUROSCIENCE SOCIETY

Marija Petronijević, Božo Knežević, Aleksa Vasić, Stefan Jakovljević, Marta Budnar, Veronika Čolić

Student section of the Serbian Neuroscience Society, Belgrade, Serbia

biologija95@gmail.com

The Student section of the Serbian Neuroscience Society was founded in 2009 in order to transfer and expand knowledge about neurosciences to a wider audience. The main method of work of the Section is a multidisciplinary approach to each topic and every problem. In this regard, the members of the Section are from the Biological, Medical, Pharmaceutical, Chemical, Philosophical and Faculty of Organizational Sciences of the University of Belgrade. The Section is a place for exchange of opinions, experiences, academic discussion on topics in the field of neuroscience, as well as everyday life. We believe that peer education is a good way to understand complex matters. For this reason, throughout the year, we learn from each other about interesting research in the field of neuroscience through interactive lectures. Knowledge acquired at the University, through the Student section, but also from the Serbian experts from the field, is passed on to the wider audience through various scientific and popular events. This requires persistent work and effort of our members; during the 10 years of existence, the Section held numerous children's workshops, as well as lectures and workshops for elementary and high school students on the territory of Belgrade and beyond. Certainly, the most important project of the Student section is Brain Awareness Week. From 2012, the Section receives a grant from the European Federation of Neuroscience Society and the DANA Foundation for the implementation of this project.

BAW5

BRAIN AWARENESS WEEK IN SERBIA

Veronika Čolić, Milica Dakić, Stefan Jakovljević

Student section of the Serbian Neuroscience Society, Belgrade, Serbia

colicveronika@gmail.com

Brain Awareness Week (BAW), a global manifestation, was held in Belgrade for the first time in 2012, in organization of Student section of the Serbian Neuroscience Society. Since then, it has become the main annual event in Section's agenda. Every year a different subject related to neuroscience is put in focus and perceived through multidisciplinary glasses. During eight years, Belgrade's BAW was answering the questions like: *why should brain be in our focus* (2012), *how can everything be related to brain, from art to science* (2013), *where could different brain waves take us* (2014), *can we see the brain as one puzzle* (2015), *how is the brain connected to seven senses* (2016), *what happens when the brain goes to the dream land* (2017), *is there consciousness in our brain* (2018), *what happens in life of one brain* (2019). Answers to these and many other questions were given to wider audience through numerous lectures, workshops, educative posters and interactive exhibitions. Each year, the program of the manifestation is adapted to people of different ages, from the youngest to the oldest ones. Through 10 years of work, Section has made co-operations with large number of Institutes, scientists, professors, faculties, laboratories and organizations, all of them contributing to successful realizations of BAW.

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Brain Awareness Week Posters

BAW6

BRAIN AWARENESS WEEK ACTIVITIES OF EGE UNIVERSITY, TURKEY – 2019

Gulgun Sengul, Burcu Balkan, Aysegul Keser, Vedat Evren

Department of Anatomy, School of Medicine, Ege University, Izmir, Turkey;
Department of Physiology, School of Medicine, Ege University, Izmir, Turkey

gulgun.sengul@gmail.com

BAW activities of Ege University, Izmir, Turkey were performed in by Gulgun Sengul, Burcu Balkan, Ayseul Keser and Vedat Evren. We had a very good BAW media coverage with a radio program on Turkish Radio (TRT Radio 1), a high number of articles on newspapers and internet on both brain health and BAW activities. A press release on BAW distributed by Ege Ajans to 3000 news and media outlets of Turkey. School activities included two high school and one primary school and one nursery school event. A neuroanatomy lab tour for 60 high school students was organized, and students had the opportunity to see the human brain specimens, and have information on brain anatomy and diseases. A movie evening open to public with a theme on artificial brain (Transcendence) with discussions hosted by a psychiatrist – Professor Ali Saffet Gonul was organized. A small neuroquiz in Ege University Hospital was made to public. Two public conferences were organized in 2019. One was by Professor Sebnem Pırıldar from Department of Psychiatry of Ege University on 'Anxiety' and the second one by Professor Ahmet Acarer from Department of Neurology of Ege University on Alzheimer's disease which was very useful for both patients and their caregivers. For the schools visited, books and brain anatomy canvas posters were given as gifts. A brain book was given to each student in the lab tour, and posters on brain health, caps and mugs were widely distributed to students and public.

BAW7

BRAIN AWARENESS WEEK OUTREACH EFFORTS AND ACTIVITIES IN ESKISEHIR, TURKEY

Ferhan Esen

Department of Biophysics, Faculty of Medicine, Eskişehir Osmangazi University

fesen@ogu.edu.tr

This year Brain Awareness Week was celebrated in Eskişehir for the 21st time. We promoted public awareness about brain through several social projects targeting; pre-school children, students, teachers, college students, general public, patients and caregivers. Over the course of 21 years we reached 45000 people through 250 public conferences, 20 panels and 8 exhibits. We visited approximately 400 local schools and 15 rural schools. Turkish versions of "It's Mindboggling!", "More Mindbogglers!" and "Mindboggling Workbook" booklets were printed and distributed to all the students. Brain Bee is very important for high school students to get acquainted with neuroscience. We organized the 12th Turkish National Brain Bee at Eskişehir Osmangazi University this year and we had 92 competitors from 31 different schools in Eskişehir, Bilecik, Kütahya, Konya and Kocaeli. Competitors had the opportunity to join lab tours and Turkish versions of books 'Brain Facts' and 'Neuroscience: Science of the Brain' were provided to them as reference. Our projects also included: dance performances, art exhibitions, poetry presentations, competitions, tree planting sessions, concerts and radio programs. We believe promoting brain health and celebrating BAW is the responsibility of the academy. It is a good opportunity to get general public and university together for the greater good of the society. Of course, the "Brain Bee" competition is an indispensable attraction for the high school students during a period when they set out their carrier.