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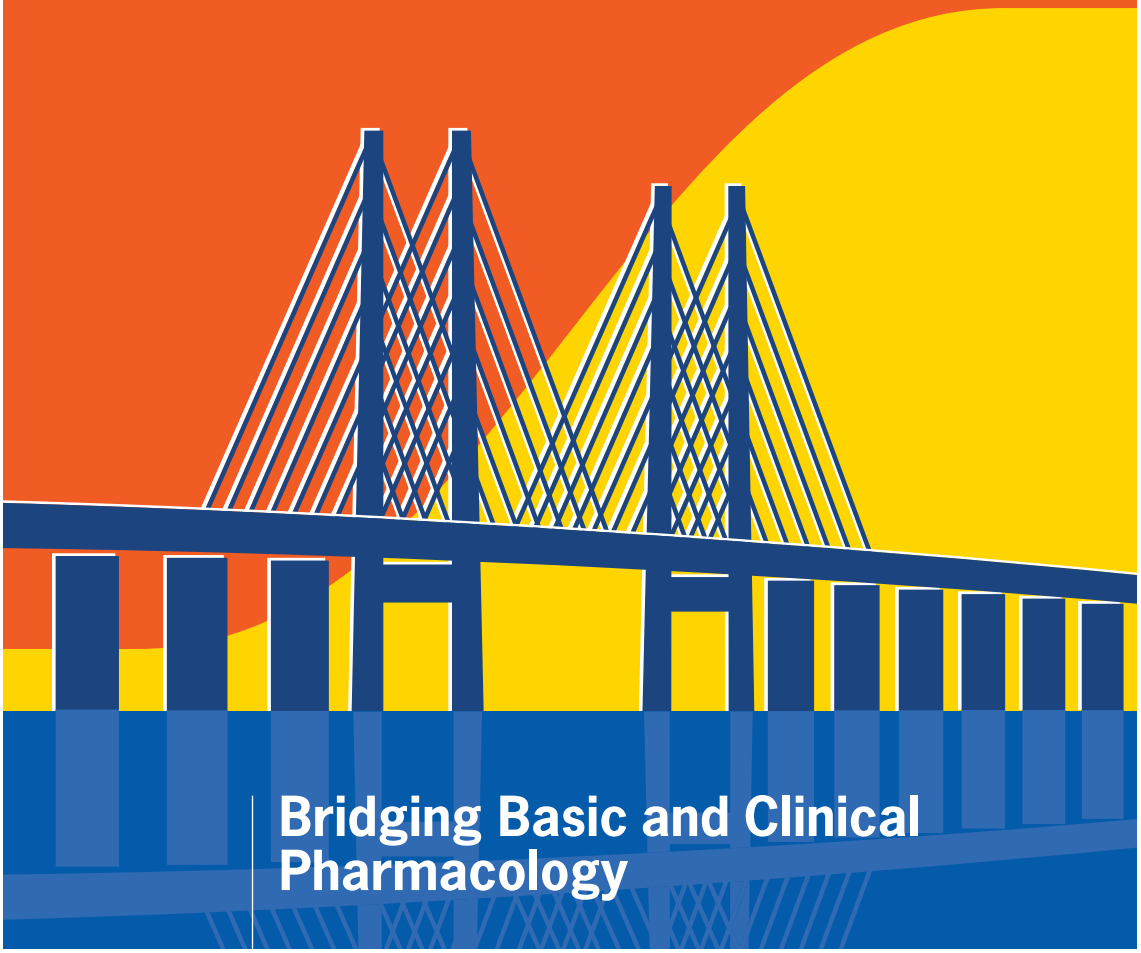

Bridging Basic and Clinical Pharmacology

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anaesthesia. The aim of this study was to test whether a continuous 96h infusion of levobupivacaine, using a Painbuster® can eliminate the need for opioid analgesia following abdominal surgery. Patients (mean ± sd age= 64 ± 5 years, n = 81) scheduled for either laparoscopic or open abdominal surgery and consented in this randomised double-blinded placebo-controlled trial, were allocated into either a treatment group (0.5% levobupivacaine infusion) or control group (0.9% saline infusion) in the Painbuster. At the end of surgery the Painbuster catheter was inserted into the incision site. Patients received opioids via a patient-controlled-analgesia (PCA) system for break-through pain. Pain scores and total opioid PCA consumption were recorded as an index of efficacy of the treatment delivered in the Painbuster. Blood samples were assayed to measure potential levobupivacaine toxicity. For those patients undergoing open surgery, the active treatment reduces pain scores, whereas in patients undergoing laparoscopic surgery there was a tendency for the active treatment to increase pain scores in comparison to the control group. There was a trend toward lower PCA consumption in patients receiving levobupivacaine for open operations, whereas there was little difference between the two treatments for patients undergoing laparoscopic surgery. The continuous infusion of levobupivacaine reduces pain scores and opioid consumption in patients undergoing open abdominal surgery.

Paper No.: 1816
FOCUSED CONFERENCE GROUP: P15 - ENDOTHELIUM IN HEALTH AND DISEASE
EXPRESSION AND FUNCTIONAL STUDIES OF SMALL - AND INTERMEDIATE CONDUCTANCE CALCIUM-ACTIVATED POTASSIUM CHANNELS IN HUMAN SMALL PULMONARY ARTERIES AND BRONCHIOLES

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Small (SK_{Ca}) and intermediate (IK_{Ca}) conductance calcium-activated potassium channels are involved in endothelium-dependent vasodilation in systemic arteries. This study investigated whether IK_{Ca} and SK_{Ca} channels are located to the human bronchial epithelium and pulmonary vascular endothelium and whether activation of these channels leads to broncho- and vasodilation. Expression of IK_{Ca} and $SK_{Ca}3$ was examined by quantitative PCR and immunoblotting, and location by immunohistochemistry. Functional studies were conducted in human small pulmonary arteries and bronchioles mounted in microvascular myographs for isometric tension recordings. $SK_{Ca}3$ protein and mRNA levels were similar in pulmonary arteries and bronchioles, while IK_{Ca} protein was highest expressed in pulmonary arteries. IK_{Ca} and $SK_{Ca}3$ immunoreaction was found both in the endothelium and epithelium. In pulmonary arteries contracted to U46619 (9,11-dideoxy-9a,11a-epoxymethanoprostaglandin $F_{2\alpha}$) and bronchioles contracted to histamine, NS309, an opener of IK_{Ca} and SK_{Ca} channels, induced concentration-dependent relaxations, which were reduced by blocking both IK_{Ca} (charybdotoxin) and SK_{Ca} channels (apamin). Relaxations evoked by a nitric oxide (NO) donor, GEA 3175, in small pulmonary arteries and by GEA 3175 and the β_2-adrenoceptor agonist, salbutamol, in bronchioles were more pronounced than NS309-evoked relaxations. These findings provide evidence for expression and a functional role of both IK_{Ca} and $SK_{Ca}3$ in the endothelium of human pulmonary arteries and epithelium of bronchioles. The location and modulation of IK_{Ca} and SK_{Ca} channels suggest that they are potential targets for treatment of pulmonary disease.

Paper No.: 1817
FOCUSED CONFERENCE GROUP: P15 - ENDOTHELIUM IN HEALTH AND DISEASE
SK_{CA} AND BK_{CA} EXPRESSION IS UPREGULATED IN PULMONARY ARTERIES FROM CHRONIC HYPOXIC RATS

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Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by abnormal constriction of pulmonary arteries, proliferative vasculopathies, and finally heart failure. The present treatments of PAH are insufficient, and therefore there is interest in new pharmacological approaches. We hypothesized that an increase in calcium-activated potassium (K_{Ca}) channel expression could be observed as a compensatory mechanism to counteract PAH. For this purpose we investigated the expression of small (SK_{Ca}), intermediate (IK_{Ca}) and large (BK_{Ca}) conductance K_{Ca} channels in lungs of normotensive/normoxic rats (n = 6) and chronic hypobaric hypoxic rats (n = 7) that develop PAH and right ventricular hypertrophy. Bronchioles and intrapulmonary arteries were isolated and the expression of K_{Ca} channels investigated by QPCR, immunohistochemistry and Western blotting. IK_{Ca} and $SK_{Ca}3$ immunoreaction was found in the arterial endothelium and bronchial epithelium. At mRNA level, K_{Ca} channels were expressed in the following order in rat bronchioles and arteries: $BK_{Ca}\beta1 > > SK_{Ca}1 > IK_{Ca} = BK_{Ca}\alpha > SK_{Ca}3 > > SK_{Ca}2$. In arteries, $BK_{Ca}\beta1$ mRNA and $BK_{Ca}\alpha$ mRNA and protein expression was upregulated by hypoxia. IK_{Ca} mRNA expression was higher in arteries than bronchioles and unaltered in tissue from chronic hypoxic rats. mRNA for $SK_{Ca}1$, $SK_{Ca}2$ and $SK_{Ca}3$ was unaltered by hypoxia, whereas $SK_{Ca}3$ protein was upregulated in arteries exposed to hypoxia. In conclusion, in pulmonary arteries from chronic hypoxic rats both $SK_{Ca}3$, $BK_{Ca}\beta1$, and $BK_{Ca}\alpha$ was upregulated. Based on these results and previous findings that K_{Ca} openers dilate pulmonary arteries, drugs that open K_{Ca} channels may be beneficial for the treatment of PAH.

Paper No.: 1793
FOCUSED CONFERENCE GROUP: P16 - NATURAL PRODUCTS: PAST AND FUTURE?
EFFECTS OF ANTIOXIDANT XANTHONES FROM *GENTIANA DINARICA* ON ACANTOSCELIDES OBTECTUS AGING *IN VIVO*

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Free radical scavenging activities of xanthones: norswertianin-1-O-primeveroside and norswertianin-8-O-primeveroside isolated from the roots of *G. dinarica* towards stable free radical 1,1-diphenyl-2-picrylhydrazyl (DPPH) were proved in the comparison to ascorbic acid. Xanthones have similar antioxidative capacity against •OH generation in metal involving Fenton reaction, when compared to synthetic analog of vitamin E - Trolox. Neither Trolox nor xanthones showed any significant capacity to scavenge •OH radical generated in Haber-Weiss-like metal-free generating system indicating their antioxidative action preferentially via sequestration of transition metals preventing •OH generation. According to its antioxidant properties, xanthones were offered as daily supplement (15 μM water solution) to an animal insect model - bean weevil Acantoscelides obtectus. Bean weevil adults have nutritional reserves for the whole lifespan and they only soak water. Treatment did not change endogenous antioxidant level in weevils, but influence the rate of aging. In females, norswertianin-8-O-primeveroside in early age slows down the rate of aging, but accelerates in the late. In males, norswertianin-1-O-primeveroside showed light, but continuous effect on slowing down the rate of aging resulting that supplemented individuals lived longer. The results showed that potential health benefits of exogenous nutritional antioxidants are combination of its individual antioxidant properties, composition, amount, metabolic fate, and the influence on antioxidant and other physiological processes, not antioxidant activity per se.