Mechanisms of redox interactions of bilirubin with copper and the effects of penicillamine

Bojana Božić[a], Jelena Korać[b], Dalibor M. Stanković[c,d], Marina Stanić[b], Ana Popović-Bijelić[e], Jelena Bogdanović Pristov[b], Ivan Spasojević[b,*], Milica Bajčetić[a,f]

[a] Department of Pharmacology, Clinical Pharmacology and Toxicology, School of Medicine, University of Belgrade, P.O. Box 38, 11000 Belgrade, Serbia
[b] Life Sciences Department, Institute for Multidisciplinary Research, University of Belgrade, Kneza Višeslava 1, 11000 Belgrade, Serbia
[c] The Vinča Institute of Nuclear Sciences, University of Belgrade, POB 522, 11001 Belgrade, Serbia
[d] Department of Analytical Chemistry, Innovation Center of the Faculty of Chemistry, University of Belgrade, Studentski trg 12-16, Belgrade, 11000, Serbia
[e] EPR Laboratory, Faculty of Physical Chemistry, University of Belgrade, Studentski trg 12-16, 11158 Belgrade, Serbia
[f] Clinical Pharmacology Unit, University Children's Hospital, 11000 Belgrade, Serbia

Toxic effects of unconjugated bilirubin (BR) in neonatal hyperbilirubinemia have been related to redox and/or coordinate interactions with Cu^{2+}. However, the development and mechanisms of such interactions at physiological pH have not been resolved. This study shows that BR reduces Cu^{2+} to Cu^{1+} in 1:1 stoichiometry. Apparently, BR undergoes degradation, i.e. BR and Cu^{2+} do not form stable complexes. The binding of Cu^{2+} to inorganic phosphates, liposomal phosphate groups, or to chelating drug penicillamine, impedes redox interactions with BR. Cu^{1+} undergoes spontaneous oxidation by O_2 resulting in hydrogen peroxide accumulation and hydroxyl radical production. In relation to this, copper and BR induced synergistic oxidative/damaging effects on erythrocytes membrane, which were alleviated by penicillamine. The production of reactive oxygen species by BR and copper represents a plausible cause of BR toxic effects and cell damage in hyperbilirubinemia. Further examination of therapeutic potentials of copper chelators in the treatment of severe neonatal hyperbilirubinemia is needed.