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MEETING ABSTRACT

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Pharmacological modulation of serum bilirubin levels: can we achieve a neuroprotective action?

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Bilirubin is an endogenous antioxidant with anti-inflammatory and anti-thrombotic activity, and is inversely correlated with risk of the outbreak of different diseases of the cardiovascular system, such as ischemic heart disease, hypertension, diabetes type II, metabolic syndrome, obesity. Bilirubin is present in various chemical forms in the blood, namely, conjugated with glucuronic acid (direct bilirubin), unconjugated bound to serum albumin (indirect bilirubin) and unconjugated-unbound (free bilirubin). Approximately 85% of the total bilirubin produced is derived from the heme moiety of hemoglobin, while the remaining 15% is produced from the red blood cell precursors. Bilirubin is normally rapidly taken up by hepatocytes where it is conjugated with glucuronic acid and thus becoming inactive but suitable for excretion. Non-conjugated serum bilirubin is 99% albumin bound. The only bioactive form is the free bilirubin, which is not measured routinely in the clinical setting, but has been recently identified to be around 10 nM in serum. Importantly, nanomolar concentrations of bilirubin can protect cells from the 10,000-fold molar excess of oxidants when both substances are added to cell cultures (*in vitro* conditions). This remarkable effect has been explained that bilirubin is acting as antioxidant, is itself oxidized to biliverdin, and then recycled by biliverdin reductase back to bilirubin. We hypothesize that modulation of serum bilirubin values is possible by pharmacological interventions acting on (i) increasing bilirubin synthesis (biliverdin reductase [BVR] induction, heme-oxygenase-1 [HO-1] induction); (ii) decreasing bilirubin metabolism (hepatic UDP-glucuronosyltransferase [UGT1A1] inhibition); (iii) decreasing bilirubin elimination (organic anion transporters [OATP] and bilitranslocase [BTL] inhibition); or (iv) by displacing it from albumin (drug interaction with bilirubin–albumin complex in blood serum). Since oxidative stress and inflammation are important pathophysiological factors in neurodegenerative diseases, the modulation of endogenous antioxidants can be a vital therapeutic approach in scavenging excess ROS, thereby preventing neuronal degeneration in a post-oxidative stress scenario. Paradoxically, high levels of serum bilirubin (>300 µmol/l) have neurotoxic effects. To exploit the novel idea of using bilirubin as endogenous neuroprotective mediator, our research group will investigate concentration-dependent effects of bilirubin on astrocytes, neurons, and microglia, as well as in whole animals in both healthy and increased oxidative stress conditions.

Keywords: bilirubin – antioxidant – neuroprotection

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