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Effect of mild hyperbilirubinemia on two *in vitro* models of metabolic syndrome

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Background: Mildly elevated serum unconjugated bilirubin has beneficial effects on oxidative stress-mediated diseases. UGT1A1 variants in Gilbert syndrome resulting in hyperbilirubinemia may confer a strong genetic advantage. Life-long genetically elevated bilirubin level is protective against the development of type 2 diabetes (T2D) and the progression of nephropathy in T2D. The prevalence of hypertension was up to 25% lower in patients with bilirubin >1 mg/dL, as serum levels of cholesterol and triacylglycerol. Serum bilirubin is negatively related to cardiovascular disease (CVD) and to incidence of metabolic syndrome. The protection provided by increased level of bilirubin appears to be largely due to its antioxidant and anti-inflammatory properties. Strategies to boost the bioavailability of bilirubin or to mimic Gilbert syndrome may prove to be an attractive intervention in cardiovascular disease and metabolic syndrome.

Aim: The aim of this paper was to study the protective role of mild hyperbilirubinemia on oxidative stress, inflammation and stress in two in vitro models of metabolic syndrome.

Methods: Heart endothelial murine H5V cells were treated with palmitic acid (PA) and kidney tubular epithelial HK-2 cells were treated with advanced glycated end products (AGE-BSA). Target genes mRNA expression, cell viability and intracellular ROS were assessed in the presence of bilirubin pretreatment or post-treatment.

Results: Twenty-four hours of PA treatment on H5V cells cause cell necrosis and mRNA induction of HO-1, IL-6, GRP78 and CHOP; treatment of 72 h induces E-Selectin, V-CAM, ICAM and iNOS. UCB pre-treatment, reverts cell necrosis, reduces CHOP, IL-6 and iNOS expression and increases HO-1. Treatment of HK-2 cells with AGE-BSA for 72h resulted in significative variation of IL-8, HIF1a, HO-1, GPX and catalase mRNA expression and increases intracellular ROS. UCB pre-treatment reverses the HO1 and GPX mRNA reduction, reduces IL-8 and HIF1a mRNA induction and ROS intracellular levels.

Conclusion: Bilirubin pretreatment modulates cell viability, ROS production and mRNA gene expression in the systems studied.

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