Abstract

This thesis focuses on the role of heme catabolic pathway in the pathogenesis of selected liver diseases. The aim was to clarify if the modulation of heme oxygenase (Hmox) and its catabolic products – especially carbon monoxide (CO) and bilirubin – affected the development and progression of liver diseases, focusing on inflammatory and cholestatic pathways.

Firstly, we discovered that the induction of *hmox1* prevented hepatocellular damage in endotoxin-induced inflammation. Furthermore, administration of CO *in vivo* in early-phase of endotoxin-induced cholestasis decreased the inflammatory cytokine production in the liver and simultaneously prevented downregulatory effect of cytokines on hepatocyte transporters resulting in hepatoprotection. For the first time, we characterized *in vivo* tissue distribution and elimination of inhaled CO in rats.

In vitro experiments and the model of extrahepatic cholestasis revealed the significant role of intracellular bilirubin in hepatocellular protection against oxidative damage which accompanies cholestatic disorders. Last but not least, *hmox1* induction by heme increased hepatocyte transporters expression and subsequently stimulated bile flow participating in conferring protection against estrogen-induced cholestasis.

Presented results demonstrate that the heme catabolic pathway is significantly involved in the cholestatic and inflammatory pathways in the liver, and its modulation might represent a potential therapeutical strategy for the treatment of liver diseases.

Key words: heme oxygenase, heme, carbon monoxide, bilirubin, liver diseases, cholestasis