ABSTRACT

Heme oxygenase (HMOX) catalyzes first and rate-limiting step in heme degradation. By its action, carbon monoxide (CO), ferrous iron and biliverdin which is subsequently reduced to bilirubin are produced. Before discovery of HMOX reaction mechanism, CO was considered only a toxic waste product without any significant importance for human organism. Bilirubin, marker of liver dysfunction, has been also exposed to similar perception. But results from past decades show that HMOX and its metabolic products play an important role in number of physiological as well as defense against pathophysiological processes.

The aim of this thesis was to clarify the role of HMOX and its metabolic products, presumably CO and bilirubin, *in vivo* and *in vitro*. We focused on the role of CO in a rat model of lipopolysaccharide-induced cholestasis. We were first to describe tissue distribution and pharmacokinetics of inhaled CO in this animal model and found out that CO inhalation is associated with anti-inflammatory and hepatoprotective effects. In a rat model of ethinylestradiol-induced cholestasis, we demonstrated the anticholestatic effect of HMOX. The induction of HMOX by its substrate heme increased the expression of liver transporters thereby increasing bile flow and simultaneously facilitated effective clearance of conjugated bile acids by kidney in cholestatic animals.

In *in vitro* and *in vivo* studies we proved that CO inhibits proliferation of pancreatic cell lines suggesting a potential of CO use as a supportive measure against this serious type of cancer with limited therapeutical options.

Mildly elevated bilirubin concentrations in serum protect organism against oxidative stress and associated diseases. In silymarin, an extract from *Silybum marianum,* we have identified flavonolignans capable of *in vitro* and *in vivo* elevation of tissue as well as systemic concentrations of unconjugated bilirubin without hepatotoxic effects. Silymarin is a widely used hepatoprotectant and induction of bilirubin, important endogenous antioxidant, can be one of the mechanisms of its action.

Results of this thesis underline the important role of HMOX and its products in metabolism and indicate a new potential therapeutic use of these compounds.

Key words: heme oxygenase, carbon monoxide, bilirubin, silymarin, UGT1A1, hepatoprotectant, cholestasis