Abstract

Changes in the iron content are among the most common metabolic diseases with a number of possible pathophysiological consequences for various body functions. The phenomenon accompanying these situations is the change in cholesterol homeostasis with possible extension to bile acids (BA), ie major executive and regulatory molecules in the metabolism of endobiotics, what can play an important role in associated organ dysfunctions. Since there was only a minimal amount of information in this area, the aim of this work was to evaluate the effect of iron overload and deficiency on the processes involved in BA turnover with the identification of involved molecular mechanisms.

The first assessed field was the evaluation of iron deficiency (ID) using a suitable rat model, where ID was induced by a specific diet. This has demonstrated a significant inducing effect on both classical and alternative pathways for BA synthesis from cholesterol. Together with the induction of cholesterol biliary secretion in ID group it led to statistically significant decrease of plasma cholesterol concentrations. The subsequent BA-dependent choleretic effect was induced by their increased liver disposition, without affecting the expression of corresponding transporters, as verified by the kinetic study with ^{3}H-taurocholate. The clinical relevance of this finding was then confirmed using human hepatic HepaRG cells, which showed the upregulation of CYP7A1 in the ID conditions. Results employing a luciferase reporter gene assay suggested that the transcriptional activation of the CYP7A1 promoter, under conditions of using iron-chelators, is independent of farnesoid X (FXR), pregnane X (PXR) or liver X (LXRα) receptors activation.

The second assessed area was the evaluation of BA and cholesterol homeostasis during iron overload. Repeated intraperitoneal administration of iron successfully evaded absorption barrier for iron in GIT. This led to the accumulation of iron (IO) in the liver. IO significantly decreased bile flow as a consequence of decreased biliary BA secretion. This decrease was associated with reduced expression of Cyp7a1 and decreased expression of Bsep transporter responsible for BA efflux into bile. However, IO did not change net BA content in faeces in response to increased conversion of BA into poorly absorbable hyodeoxycholic acid. In addition, IO increased plasma cholesterol concentrations, which corresponded with reduced Cyp7a1

expression and increased expression of HmgCR, the rate limiting enzyme for cholesterol *de novo* synthesis.

The results of this dissertation suggest that reduced or increased iron content in the liver has a complex effect on bile formation and bile acid and cholesterol homeostasis. A key role in these effects plays the modulation of Cyp7a1, a major enzyme in the bile acid synthesis process. However, parallel changes in hepatic uptake, synthesis and biliary cholesterol secretion are also important. These findings contribute to the understanding of the pathophysiology of clinically frequently occurring iron-altered situations, such as iron deficiency, especially during its increased loss or excessive need during pregnancy, and excessive liver accumulation associated with fatty liver during obesity.