Summary

Dynamics of changes in bile acid metabolomics in estrogen-induced cholestasis

Bile acids are essential endobiotics with numerous exocrine and endocrine functions. In this dissertation, we evaluate three factors that were suspected of modifying bile acid metabolomics: i) the effect of metformin in estrogen-induced cholestasis, ii) the role of MRP2 (multidrug resistance-associated protein 2) protein in the described risk of more frequent intrahepatic cholestasis in pregnancy, and iii) the excessive iron accumulation in the liver.

Metformin has been tested for its potential use in women with gestational diabetes mellitus (GDM) who have a higher incidence of intrahepatic cholestasis (ICP). As an ICP model, we used experimental cholestasis induced in mice by administration of ethinylestradiol. Administration of metformin in this situation significantly increased bile acid concentrations in the systemic circulation, which reached values considered significantly toxic in pregnant women. These data suggest that the possibility of developing ICP is accentuated when metformin is used in pregnant women.

In another study, we demonstrated that the MRP2 transporter plays a significant role in biliary bile acid elimination and that the genetic defect itself caused an increase in the plasma concentrations in rats. Estrogen administration to MRP2-negative rats resulted in a much more pronounced increase in bile acid plasma concentrations than was detected in estrogen cholestasis in control animals. Thus, for the first time, our experimental data explained the mechanisms of the more frequent occurrence of ICP in pregnant women with MRP2 transporter deficiency.

The third factor studied was the effect of excess iron in the liver on bile acid metabolomics. The model used was repeated parenteral iron administration in rats. Subsequent analysis revealed significantly reduced biliary bile acid secretion in these animals due to decreased synthesis by the reduced CYP7A1 enzyme and the hepatic expression of the crucial elimination transporters NTCP, BSEP, and MRP2. Significant systemic accumulation of bile acid was prevented by reducing reabsorption in the ileum. This effect was probably due to the increased synthesis of poorly absorbable hyodeoxycholic acid via the altered intestinal microbiome. In this study, it was possible to describe the changes in the bile acid metabolomics due to iron accumulation. These changes may contribute to the developing liver damage that accompanies iron storage in this organ.