Summary

Bile acids (BAs) play a key role in the cholesterol metabolism and homeostasis of nutrients, especially fats. Impaired bile acid turnover can lead to retention with manifestations of toxicity, which can also be observed in non-alcoholic fatty liver disease, especially if its the more severe form, non-alcoholic steatohepatitis (NASH), develops. Since the accumulation of BA may contribute to the development of NASH, it is important to look for a treatment that can favorably affect both NASH pathology and BA homeostasis. At the same time, it is advisable to avoid the administration of drugs that could worsen the retention of BA in the body in the given situation. In our study, we analyzed the ability to induce changes in BA homeostasis with carvedilol and atorvastatin, drugs used in clinical practice in the treatment of cardiovascular complications accompanying the metabolic syndrome and NASH. At the same time, the potential cholestatic effect of labetalol, a drug with an identical mechanism of action as carvedilol, was analyzed.

Carvedilol, an α_1 and β-adrenoceptor antagonist, may in rare cases induce symptoms of cholestasis. However, in patients with cirrhosis and portal hypertension, carvedilol as the drug of choice reduces the incidence of vascular complications. We were able to demonstrate that carvedilol provoked cholestasis symptoms with increased plasma levels of BAs in healthy mice. This accumulation was caused by the reduction of the Ntcp transporter through the blockade of the β-adrenoreceptor-cAMP-Epac1 pathway. In NASH, on the other hand, carvedilol showed a positive effect on hepatic fat accumulation and reduced the intensity of inflammation and fibrosis. Consequently, carvedilol did not worsen the BA accumulation in mice with NASH, but it changed the profile of individual BAs in favor of hydrophilic representatives. This study thus clarified the significant positive effects of carvedilol in NASH and thus supports the possibility of using this substance in clinical practice.

The mouse model of NASH was also used in the second study to analyze the effect of atorvastatin. It was significant that atorvastatin reduced the plasma concentrations of BAs in the control group. This reduction was a consequence of the repression of liver enzymes synthesizing BAs, and the Asbt transporter ensuring reabsorption of BAs from intestinal contents, which led to an increase in fecal BA excretion. In mice with NASH, the effect of atorvastatin on BA was minor. However, it was interesting to see an increase in the proportion of deoxycholic acid after atorvastatin administration in plasma, bile and faeces through the reduction of enzymes for the synthesis of BAs via an alternative pathway. The diagnostic value of deoxycholic acid determination during statin therapy needs to be further investigated. However, atorvastatin significantly reduced hepatic fat deposition and the degree of inflammation in NASH mice by affecting NF-κB pro-inflammatory signaling. The explanation of the involved mechanisms in our study supports the safe use of statins in patients with NASH, which has recently begun to be recommended.

In the third study, we analyzed the effect of α_1 and β-adrenergic receptor blockade by means of labetalol in experimental estrogen-induced cholestasis, a model of intrahepatic cholestasis during pregnancy. Such a situation can occur in clinical practice if a pregnant woman with preeclampsia is treated with labetalol and at the same time has intrahepatic cholestasis with high levels of BAs, which represent the main risk of damage to the fetus. The analysis of BAs in our study confirmed an increase in their plasma levels in the group with simultaneous administration of estrogen and labetalol due to the induction of the Mrp4 transporter. Labetalol was able to increase plasma BA levels even in a mouse transgenic model of preeclampsia with high levels of soluble endoglin and estrogen-induced cholestasis. The estrogen-induced cholestasis itself leads to an increase in the levels of soluble endoglin in the plasma and thus promotes the development of preeclampsia. This study thus brought an important finding that labetalol may not be a suitable drug in women with preeclampsia and a predisposition to cholestasis, as it can significantly worsen the accumulation of BAs in the plasma.