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MEETING ABSTRACTS

ABSENCE OF MULTIDRUG RESISTANCE-ASSOCIATED PROTEIN 2 INCREASES THE PLASMA CONCENTRATIONS OF BILE ACIDS IN RATS WITH ESTROGEN-INDUCED CHOLESTASIS

Fatemeh Alaei Faradonbeh [1], Hana Lastuvkova [1], Jolana Schreiberova [1], Milos Hroch [2], Zuzana Nova [1], Martin Uher [2], Petra Hirsova [3], Petr Pavek [4], Stanislav Micuda [1]

[1] Charles University, Department of Pharmacology, Faculty of Medicine,500 02, Hradec Kralove, Czechia.
[2] Charles University, Department of Biochemistry, Faculty of Medicine,500 02, Hradec Kralove, Czechia.
[3] Mayo Clinic, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, 559 05, Minnesota, United States.
[4] Charles University, Department of Pharmacology and Toxicology, Faculty of Pharmacy.500 05, Hradec Kralove, Czechia.

Multidrug resistance-associated protein 2 (Mrp2) is the crucial transporter for the biliary secretion of anionic compounds. The genetically determined absence of this transporter may occur in humans, causing conjugated hyperbilirubinemia and increased risk of intrahepatic cholestasis of pregnancy (ICP). The ICP threatens fetuses with adverse pregnancy outcomes due to increased bile acids (BAs) plasma concentrations. This study aimed to characterize BAs metabolomics in Mrp2 deficiency and ICP. Cholestasis was induced in Mrp2-deficient and wild-type rats by ethinylestradiol as a model of ICP. BAs were analyzed in plasma, bile, and stool to describe their metabolomics together with liver and intestinal enzymes and transporters responsible for BAs enterohepatic recycling. Mrp2-deficiency reduced the biliary secretion of BAs and increased their plasma concentrations in part due to increased BAs efflux from hepatocytes to the blood via upregulated Mrp3 and Mrp4 transporters. The intestinal BAs reabsorption was also reduced in these rats due to downregulated ileal sodium/bile acid cotransporter. The activation of constitutive androstane receptor-nuclear factor erythroid 2 related factor 2 pathway by accumulating bilirubin might be responsible for observed changes in BAs metabolomics in Mrp2-deficient rats. The plasma concentrations of BAs were further increased by ethinylestradiol administration in Mrp2-negative rats due to reduced BAs uptake and increased hepatocyte efflux via reduced Slco1a1 and upregulated Mrp4 transporters. Our results confirmed the hypothesis that impaired Mrp2 transporter predisposes to increased plasma concentrations in estrogen-induced cholestasis due to complex changes in liver transporting proteins. We, therefore, recommend regular monitoring of BAs in the plasma of pregnant women with conjugated hyperbilirubinemia.

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Keywords: Multidrug resistance-associated protein 2; Bile acids; Ethinylestradiol