Endogenous Coproporphyrin I and III are Altered in Multidrug Resistance-Associated Protein 2-Deficient (TR; -;) Rats.

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Author(s) Bezençon, Jacqueline; Saran, Chitra; Hussner, Janine; Beaudoin, James J; Zhang, Yueping; Shen, Hong; Fallon, John K; Smith, Philip C; Meyer zu Schwabedissen, Henriette E; Brouwer, Kim L R
Author(s) at UniBasel Meyer zu Schwabedissen, Henriette ; Hussner, Janine ;
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Recent studies have focused on coproporphyrin (CP)-I and CP-III (CPs) as endogenous biomarkers for organic anion transporting polypeptides (OATPs). Previous data showed that CPs are also substrates of multidrug resistance-associated protein (MRP/Mrp) 2 and 3. This study was designed to examine the impact of loss of Mrp2 function on the routes of excretion of endogenous CPs in wild-type (WT) Wistar compared to Mrp2-deficient TR; -; rats. To exclude possible confounding effects of rat Oatps, the transport of CPs was investigated in Oatp-overexpressing HeLa cells. Results indicated that CPs are substrates of rodent Oatp1b2, and that CP-III is a substrate of Oatp2b1. Quantitative targeted absolute proteomic (QTAP) analysis revealed no differences in Oatps, but an expected significant increase in Mrp3 protein levels in TR; -; compared to WT rat livers. CP-I and CP-III concentrations measured by LC-MS/MS were elevated in TR; -; compared to WT rat liver, while CP-I and CP-III estimated biliary clearance was decreased 75- and 840-fold in TR; -; compared to WT rats, respectively. CP-III concentrations were decreased 14-fold in the feces of TR; -; compared to WT rats, but differences in CP-I were not significant. In summary, the disposition of CPs was markedly altered by loss of Mrp2 and increased Mrp3 function as measured in TR; -; rats.

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