FUNCTIONAL CHARACTERIZATION, TISSUE DISTRIBUTION AND IMMUNOLOCALIZATION OF RAT H⁺/ORGANIC CATION ANTIPORTER MATE1

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H⁺/organic cation antiport system, localized at the brush-border membranes of proximal tubules, plays an important role for renal tubular secretion of organic cations, in conjunction with membrane potential-dependent organic cation transporters (OCTs) localized at the basolateral membranes. Recently, human and mouse orthologues of the multidrug and toxin extrusion (MATE) family have been identified as H⁺/organic cation antiporters. Based on these sequence information, we isolated rat (r) MATE1 cDNA by PCR cloning, and examined the tissue distribution and transport characteristics 1). rMATE1 mRNA was expressed abundantly in the kidney and placenta, but not expressed in the liver. Real-time PCR analysis of microdissected nephron segments showed that rMATE1 was primarily expressed in the proximal convoluted and straight tubules. The uptake of a prototypical organic cation tetraethylammonium (TEA) by rMATE1-expressing HEK293 cells was stimulated by intracellular acidification by NH₄Cl treatment. rMATE1 transported organic cations such as cimetidine and metformin, but not p-aminohippurate, a typical organic anion. Using antibody against rMATE1, immunoreactive protein at about 70 kDa was detected in the brush-border membranes by Western blot analysis. Furthermore, immunohistochemical analyses showed that rMATE1 was localized at the brush-border membranes of renal proximal tubules. These findings indicate that rMATE1 is expressed at the brush-border membranes of proximal tubules and can mediate the transport of various organic cations by the oppositely directed H⁺ gradient as a driving force.


ROLE OF BILE ACID ABSORPTION IN THE REGULATION OF HEPATIC BILE ACID LEVELS

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Hepatic bile acid levels are tightly regulated through control of bile acid biosynthesis, absorption and excretion. The farnesoid X receptor (FXR) plays a crucial role in bile acid regulation. Hepatic bile acid levels are higher in FXR-null mice fed a control diet or a cholic acid (CA) diet than in wild-type mice. FXR-mediated enhancement of biliary bile acid output rates prevents the accumulation of hepatic bile acids in wild-type mice fed a CA diet. However, a possible influence on intestinal absorption cannot be excluded. We have examined the intestinal absorption of bile acids in FXR-null and the wild-type mice. The ileal absorption rate of taurocholateoxycholic acid (TCDDA) was measured in portal blood 10 min after TCDDA injection into the ileal loop. The absorption rate was significantly lower in the wild-type mice fed a control diet than that in FXR-null mice. CA feeding resulted in decreased absorption rates and mRNA levels of ileal apical sodium-dependent bile acid transporter in wild-type mice but not in FXR-null mice. Hepatic bile acid levels and the absorption rates were decreased in FXR-null mice co-treated with CA and cholesterol compared to the mice treated with only CA. However, the biliary bile acid output rates were not increased in co-treated FXR-null mice compared to mice treated with only CA. These results suggest the possibility that the intestinal bile acid absorption is a rate-limiting step in the regulation of hepatic bile acid levels.