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Hepatobiliary Transport: Mechanisms, QSAR and Regulation

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Over the last 5 years or so, there has been a significant increase in the molecular characterization of transport proteins in animals and man. This has led to a better understanding of the importance of such transport proteins in the disposition of endogenous compounds, drugs and other xenobiotics in many organs such as the intestine, liver, kidney and brain. The liver plays a key role in the clearance and excretion of many endogenous as well as xenobiotic substances and hepatobiliary excretion of drugs from blood, through the hepatocyte, and into the bile can be considered a three-step process; a) the uptake of drugs from blood into the hepatocyte through the sinusoidal (basolateral) membrane, b) transfer of drugs to metabolic sites and/or the biliary canalicular membrane inside the hepatocyte, c) excretion in to bile through the canalicular membrane. A wide variety of active transporters are known to be present at both the sinusoidal and the canalicular membrane to mediate the hepatobiliary transport. Many of the functionally predicted drug elimination systems in liver have now been cloned and characterized. A summary of the major hepatic sinusoidal and canalicular membrane transporters involved in transport of therapeutic drugs is provided in Fig. 1.

Uptake Transporters

Important carrier families for uptake of drugs and endogenous compounds in liver are the Na^+-taurocholate transporting polypeptide (Ntcp/NTCP), the organic anion transporting polypeptides (Oatps/OATPs), the organic cation transporters (OCTs), and the organic anion transporters (OATs). Ntcp/NTCP is exclusively expressed at the basolateral domain of hepatocytes and mediates uptake of conjugated bile acids and few sulfated steroids. Oatps/OATPs are expressed at the sinusoidal membrane of hepatocytes where they mediate uptake of large organic anions, organic cations and uncharged substrates. In contrast, OCTs and OATs are important for uptake of small organic cations and small organic anions at the basolateral membrane of proximal tubular cells. rOCT1 and hOCT1 are expressed at the sinusoidal membrane of hepatocytes, but although small cations are rapidly taken up into rat hepatocytes, they do not appear in bile. Instead, after primary uptake they are effluxed into the bloodstream and excreted by the kidneys. rOAT2 and rOAT3 are also expressed at the sinusoidal membrane of

hepatocytes, but in contrast to the kidney-specific rOAT1, their substrate specificities overlap with the Oatps.

Excretion Transporters

Excretion of drugs and endogenous compounds across the canalicular membrane into bile is mainly mediated by ATP-dependent transporters which belong to the ABC transporter superfamily. Within this superfamily, the multidrug resistance protein (Mdr/MDR) and the multidrug resistance-associated protein (Mrp/MRP) subfamilies are important for drug excretion in liver.

Mdr1/MDR1 (*ABCB1*) transports a wide variety of structurally unrelated compounds such as vinca alkaloids, anthracyclines, cyclosporin, steroid hormones, digoxin and miscellaneous hydrophobic organic cations. **Mdr2/MDR3** (*ABCB4*) translocates phospholipids such as phosphatidylcholine from the inner to the outer leaflet of the membrane from where it can be extracted by bile acids into bile. In addition to phospholipids, MDR3 was shown to transport a subset of MDR1 substrates such as digoxin, paclitaxel and vinblastine, although with low transport rates. Bile salt export pump (**Bsep/BSEP**, *ABCB11*) transports bile acids across the canalicular membrane. Mrps/MRPs transport mainly amphipathic organic anions. **Mrp1/MRP1** (*ABCC1*) is expressed at the basolateral membrane of hepatocytes and transports glutathione-*S* conjugates, oxidized glutathione, glucuronate and sulfate conjugates such as leukotriene C4 and estradiol-17β-glucuronide. **Mrp2/MRP2** (*ABCC2*) is expressed at the canalicular membrane of hepatocytes and is the major biliary excretiopn route of a broad variety of organic anions. The substrate specificity of Mrp2/MRP2 is almost identical to Mrp1/MRP1 and the protein is responsible to a large extent for the bile salt independent bile flow. Prototypic high-affinity substrates of MRP2 include bilirubinmonoglucuronide, bilirubindiglucuronide, and leukotriene C4.

Mrp3/MRP3 (*ABCC3*) is most closely related to Mrp1/MRP1 and has a similar substrate specificity as Mrp1/MRP1 except for glutathione-S conjugates which are poor substrates for Mrp3/MRP3 and of bile acids which are not transported by Mrp1/MRP1. The expression of both Mrp1/MRP1 and Mrp3/MRP3 is low under normal conditions, but it was shown that Mrp3/MRP3 is upregulated in cholestatic liver disease to compensate for the impaired biliary secretion of organic anions. **Mrp5/MRP5** (*ABCC5*) has been detected in numerous tissues including liver and mediates ATP-dependent cAMP, cGMP, DNP-SG, and GSH. **Mrp6/MRP6** (*ABCC6*) are also expressed at the basolateral membrane of hepatocytes and an unusual member of MRP subfamily. Mrp6 does not transport any of the typical MRP substrates, such as DNP-SG, LTC4, or $E_2$17βG. The only substrate identified so far is the endothelin receptor antagonist BQ-123.

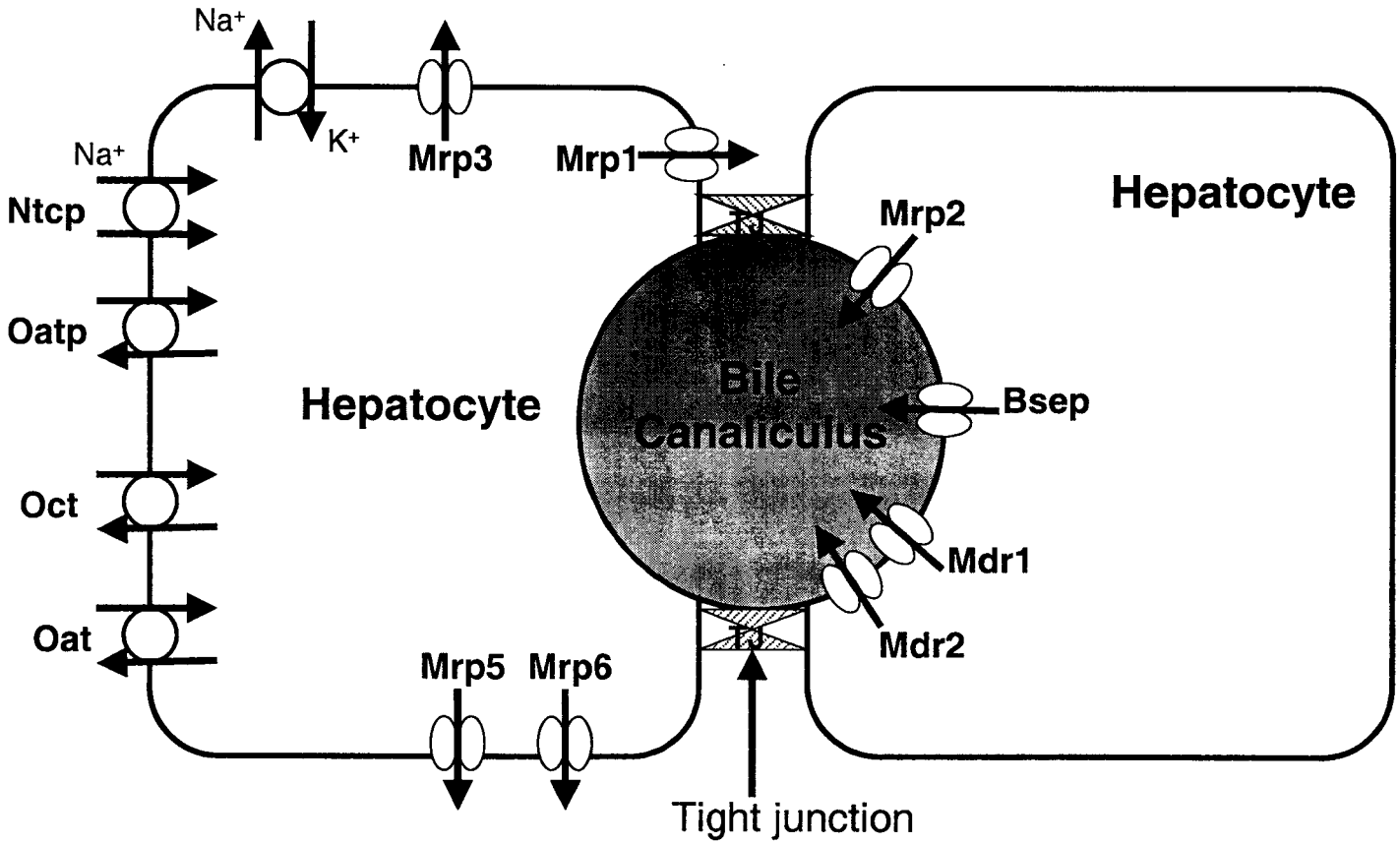

Fig 1. Sinusoidal and Canalicular Transporters in the Liver