Molecular mechanisms of cholestasis

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Received February 2, 2006; accepted April 5, 2006
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Summary. Recent progress has enhanced our understanding of the pathogenesis of cholestatic liver diseases. Mutations in genes encoding for hepatobiliary transport systems can cause hereditary cholestatic syndromes and exposure to cholestatic agents (drugs, hormones, inflammatory cytokines) can lead to reduced expression and function of hepatic uptake and excretory systems in acquired forms of cholestasis. In addition to transporter changes which cause or maintain cholestasis, some alterations in transporter gene expression can be viewed as hepatoprotective mechanisms aimed at reducing intrahepatic accumulation of toxic biliary constituents such as bile acids and bilirubin. Alternative excretion of bile acids via the basolateral membrane into the systemic circulation facilitates the renal elimination of bile acids into urine. Moreover, increased bile acid hydroxylation, sulfation and glucuronidation by phase I and II metabolizing enzymes renders bile acids more hydrophilic and less toxic. These molecular changes are mediated by specific nuclear receptors which are regulated by bile acids, proinflammatory cytokines, drugs, and hormones. In addition to transcriptional changes, reduced transporter protein insertion to or increased retrieval from the cell membrane as well as other mechanisms such as altered cell polarity, disruption of cell-to-cell junctions and cytoskeletal changes are involved in the pathogenesis of cholestasis. Understanding the detailed mechanisms regulating expression of transport systems and enzymes is essential for the development of novel therapeutic agents. Such future approaches could specifically target nuclear receptors thus restoring defective transporter expression and supporting hepatic defense mechanisms against toxic bile acids.

Key words: Cholestasis, jaundice, bile acids, bilirubin, ATP-binding cassette transporters, nuclear receptors, ursodeoxycholic acid, rifampin.
Introduction

Bile secretion plays a pivotal role in liver physiology because it serves as an important excretory route for many xenobiotics (e.g., bile acids, bilirubin, cholesterol, phospholipids and drugs). Furthermore, bile acids are essential for the digestion and absorption of lipids from the intestinal lumen. Recently, major advances have been made in the molecular identification of membrane transport proteins in liver and intestine that control bile formation [1, 2]. The liver comprises a broad range of specific uptake and export systems for various biliary compounds, which are localized to the basolateral (sinusoidal) and canalicular (apical) membrane of the hepatocyte (Fig. 1). Bile is primarily formed by canalicular excretion of bile acids and non-bile acid organic anions via ATP-binding cassette (ABC) transporters. These osmotically active compounds induce passive movement of water through the tight junctions. Bile acids are the main solutes in bile and are considered to be the major osmotic driving force in the generation of bile flow (“bile acid-dependent bile flow”). Biliary bile acids then induce canalicular phospholipid and cholesterol secretion and form mixed biliary micelles. Bile-acid-independent processes also contribute to bile production (“bile acid-independent bile flow”), consisting mainly of the canalicular secretion of reduced glutathione and the excretion of bicarbonate. This canalicular primary bile is further modified by absorptive and secretory processes along the biliary tree [3]. Bile acids undergo an enterohepatic circulation which consists of their continuous hepatocellular canalicular secretion, active reabsorption in the terminal ileum and hepatic basolateral reuptake (Fig. 1). Thus, this bile salt pool circulates 6–10 times per day in humans [4].

Cholestasis may either result from a functional defect in bile formation at the level of the hepatocyte or from impairment in bile secretion and flow at the bile duct level. Exposure to cholestatic injury (e.g., drugs, hormones, pro-inflammatory cytokines, biliary obstruction/destruction) or hereditary mutations in transport systems (Fig. 1) results in reduced expression and function in hepatobiliary transport proteins [2].

Hereditary transporter defects

Mutations of transporter genes can result in hereditary syndromes of progressive familial intrahepatic cholestasis (PFIC) (Fig. 2). Four subtypes (PFIC-1–4) of these autosomal recessively inherited disorders in infants and children have been described. PFIC-1 (also known as Byler disease) is caused by a mutation of the putative aminophospholipid transporter FIC1 (Fig. 2) and leads to the development of liver cirrhosis in early childhood [5]. This disease is characterized by elevated serum bile acid and low gamma-glutamyl transpeptidase (GGT) levels. The exact pathomechanism of this disease is unknown, since the role for FIC1 in bile secretion is not entirely clear. FIC1 might contribute to the elimination of hydrophobic secondary bile acids such as toxic lithocholic acid. Benign recurrent intrahepatic cholestasis (BRIC-1, Summerskill syndrome) is also caused by mutations of FIC1 and is characterized by recurrent episodes of cholestasis not leading to liver cirrhosis [5]. Both syndromes are associated with extrhepatic manifestations such as diarrhea, bile acid malabsorption, pancreatitis and nephrolithiasis, which can be explained by expression of FIC1 in these tissues. Mutations of the bile salt export pump (BSEP), the major canalicular bile acid export system, causes PFIC-2 [6] (Fig. 2). The clinical course is similar to PFIC-1, however, extrhepatic manifestations are absent, since BSEP expression is restricted to the liver. More moderate courses of this disorder cause a variant of benign intrahepatic recurrent cholestasis (BRIC-2). PFIC-3 presents with high levels of GGT and is caused by mutations of multidrug resistance protein MDR3, which is a phospholipid export pump [7] (Fig. 2). Phospholipids in bile are required for the formation of mixed micelles with bile acids and cholesterol to protect the bile duct epithelia from the detergent properties of bile acids.