

Bile Acid Biology, Pathophysiology, and Therapeutics

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Bile acids are synthesized from cholesterol exclusively in the liver and function as physiological detergents that facilitate biliary cholesterol excretion. Bile acids are stored in the gallbladder as bile salts. After meal intake, bile acids are released into the gastrointestinal tract to aid in absorption of nutrients, dietary fats, steroids, vitamins, and drugs. Recent advances in basic research have identified bile acids as nutrient sensors and metabolic integrators that activate farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5) to regulate lipid, glucose, and energy metabolism, and maintain metabolic homeostasis.¹ This review will briefly cover bile acid physiology and synthesis, pathophysiology of cholestatic liver diseases and nonalcoholic fatty liver disease (NAFLD), and bile acid–based therapy for liver-related diseases.

There are two major bile acid synthesis pathways in the liver.² The classic pathway is initiated by cholesterol 7 α -hydroxylase (CYP7A1) and synthesizes the two primary bile acids in humans, chenodeoxycholic acid (CDCA) and cholic acid (CA), the latter of which requires sterol 12 α -hydroxylase (CYP8B1) (Fig. 1). Serum 7 α -hydroxy-4-cholesten-3-one (C4), a common precursor for CA and CDCA, is used as an indicator of bile acid synthesis rate. The alternative pathway is initiated by sterol 27-hydroxylase (CYP27A1), which synthesizes oxidized sterols, followed by oxysterol 7 α -hydroxylase (CYP7B1). Bile acids are conjugated to taurine or glycine to increase solubility for biliary secretion. In the colon, gut bacterial bile salt hydrolase (BSH) deconjugates bile acids, and 7 α -dehydroxylase removes the 7 α -HO-group from CA and CDCA

Abbreviations: ASBT, apical sodium-dependent bile salt transporter; BSEP, bile salt export pump; BSH, bile salt hydrolase; C4, 7 α -hydroxy-4-cholesten-3-one; CA, cholic acid; CDCA, chenodeoxycholic acid; CYP27A1, sterol 27-hydroxylase; CYP7A1, cholesterol 7 α -hydroxylase; CYP7B1, oxysterol 7 α -hydroxylase; CYP8B1, sterol 12 α -hydroxylase; DCA, deoxycholic acid; FGF, fibroblast growth factor; FGFR4, FGF receptor 4; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide 1; ICP, intrahepatic cholestasis of pregnancy; LCA, lithocholic acid; MDR3, multidrug-resistant protein 3; MRP, MDR resistance-associated protein; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NTCP, Na⁺-dependent taurocholate cotransporting peptide; OST, organic solute transporter; PBC, primary biliary cirrhosis; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis; SHP, small heterodimer partner; T2D, type 2 diabetes; TGR5, Takeda G protein-coupled receptor 5; TJP2, tight junction protein 2; UDCA, ursodeoxycholic acid.

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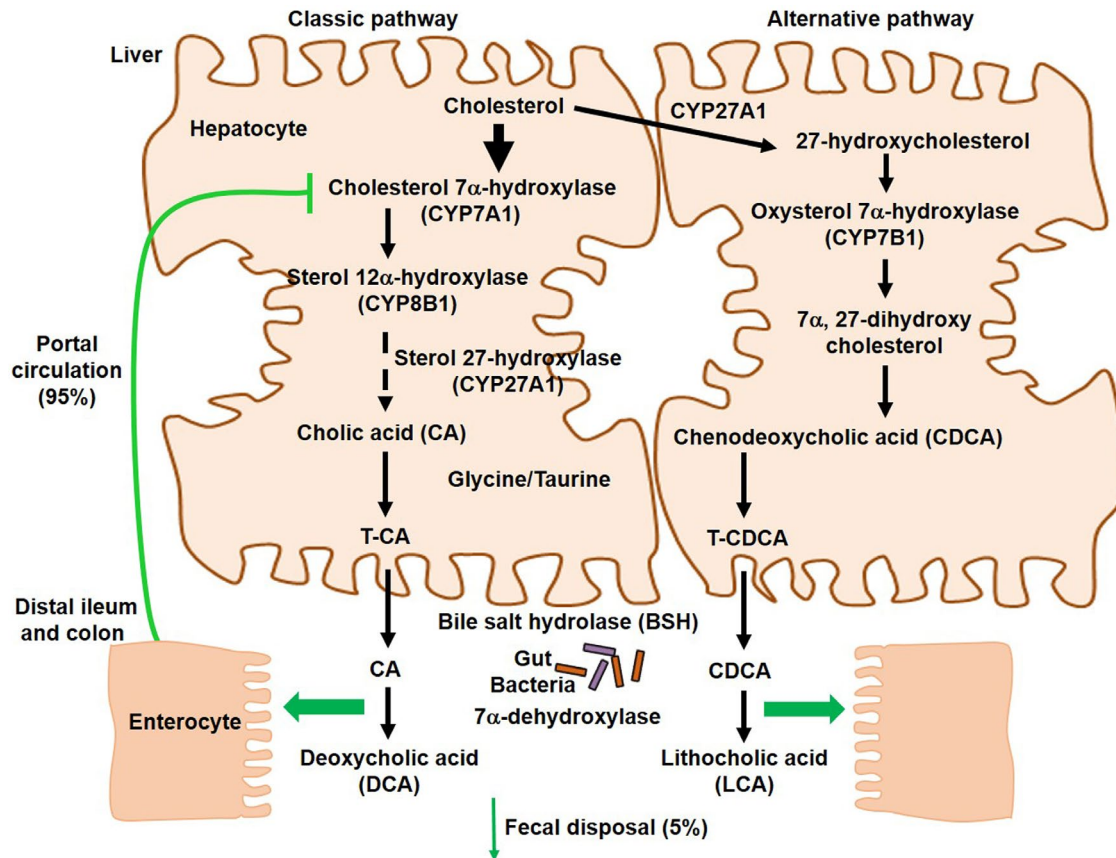


FIG 1 Bile acid synthesis. Bile acids are synthesized from cholesterol in the liver. A total of 17 enzymes located in the cytosol, endoplasmic reticulum, mitochondria, and peroxisomes of hepatocytes are involved in bile acid synthesis. The classic pathway is initiated by the rate-limiting enzyme, CYP7A1, to synthesize the two primary bile acids in humans, CA and CDCA. CYP8B1 is required for CA synthesis, and mitochondrial CYP27A1 catalyzes a steroid side-chain oxidation. The alternative pathway is initiated by CYP27A1, followed by CYP7B1. A common precursor of CA and CDCA, C4, is used as a serum marker for bile acid synthesis rate. After synthesis, bile acids are conjugated to the amino acids taurine or glycine for biliary secretion. In the distal ileum and colon, gut bacterial BSH deconjugates the conjugated bile acids, and bacterial 7 α -dehydroxylase removes the 7 α -hydroxyl group to convert CA and CDCA to the secondary bile acids DCA and LCA, respectively. The classic pathway is the major pathway for daily synthesis of about 80% of the bile acids in humans, whereas the alternative pathway synthesizes about 20%. Most bile acids (~95%) are reabsorbed in the ileum and transported via portal blood to the liver to inhibit bile acid synthesis. A small amount of bile acids (~5%) lost in feces is replenished by *de novo* synthesis.

to form the secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA), respectively. Conjugated CA, CDCA, and DCA are secreted into portal blood circulation and reabsorbed into the liver to inhibit bile acid synthesis.

Emerging research in bile acid metabolism in the past three decades has contributed significantly to our current understanding of the roles of FXR and TGR5 in the pathophysiology of liver-related diseases. FXR is highly expressed in the gastrointestinal system and plays a central role in the regulation of enterohepatic circulation of bile acids. Bile acids activate FXR to induce bile salt export pump (BSEP), which secretes bile acids into bile canaliculi, forming mixed micelles with cholesterol and phospholipids (Fig. 2). In the ileum, most conjugated

bile acids are reabsorbed by apical sodium-dependent bile salt transporter (ASBT). FXR also induces sinusoidal organic solute transporter α/β (OST α /OST β) to secrete bile acids into the portal circulation. Bile acids are reabsorbed from portal blood into hepatocytes by sodium-dependent taurocholate transporting peptide (NTCP). Bile acid synthesis is tightly regulated by complex mechanisms to maintain low levels of bile acids in the liver. In the liver, FXR inhibits CYP7A1 gene transcription indirectly via inducing the negative nuclear receptor small heterodimer partner (SHP). In the intestine, FXR induces fibroblast growth factor 19 (FGF19), which activates liver FGF receptor 4 (FGFR4) to inhibit CYP7A1 via extracellular signal-regulated kinase 1/2 signaling. TGR5 is expressed in many tissues, except hepatocytes. Activation of TGR5

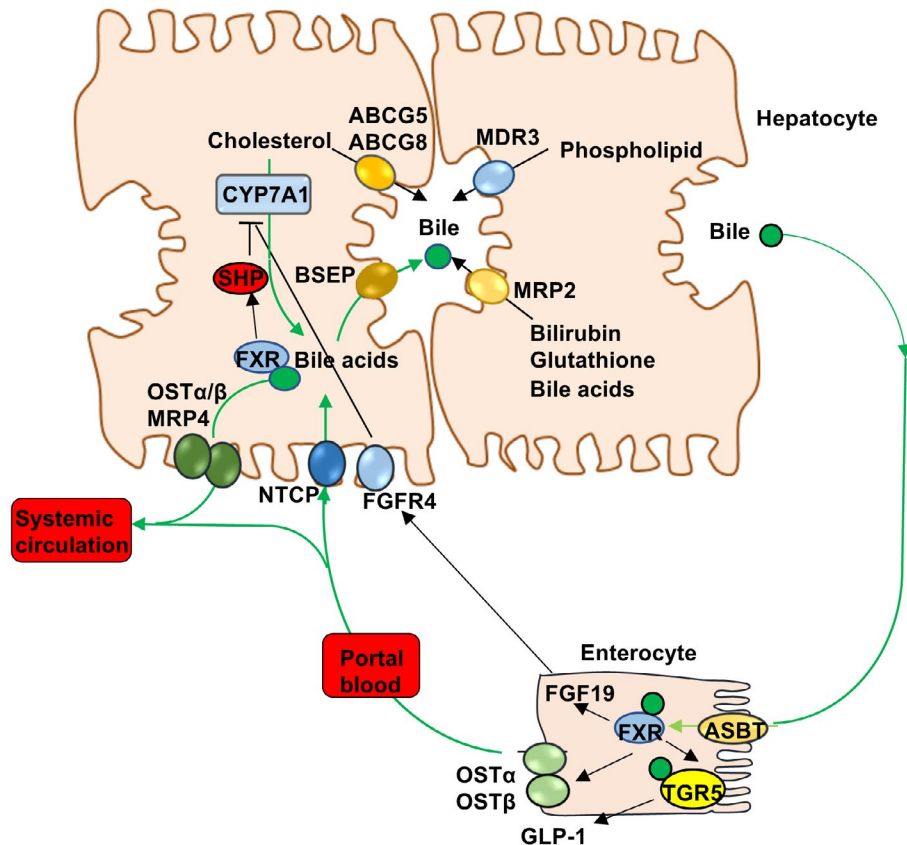


FIG 2 FXR regulation of bile acid synthesis and enterohepatic circulation of bile acids. In hepatocytes, FXR induces SHP, which inhibits transcription of CYP7A1 and bile acid synthesis. FXR induces BSEP, which actively excretes bile acids into bile. Bile acids also facilitate biliary cholesterol secretion via ATP binding cassette family G5 and G8 transporters (ABCG5, ABCG8). MDR3 (ABCB4) transports phospholipids into bile, whereas MRP2 transports bilirubin, glutathione, and unconjugated bile acids. In the ileum, bile acids are reabsorbed into enterocytes via ASBT. Intestinal FXR induces sinusoidal OST α /OST β heterodimer to efflux bile acids into the portal blood circulation to the liver, where NTCP takes up bile acids into hepatocytes. Intestinal FXR induces FGF19, which circulates to the liver and binds to hepatic FGFR4, inhibiting bile acid synthesis. Bile acids also activate FXR to induce OST α /OST β and MRP4 to efflux bile acids as an adaptive response to cholestasis. FXR induces TGR5 expression in enteroendocrine cells to stimulate secretion of glucagon-like peptide 1 (GLP-1), which stimulates insulin secretion from the pancreas and improves insulin sensitivity, and also promotes adipose tissue browning and energy metabolism.

by secondary bile acids in enteroendocrine cells stimulates secretion of glucagon-like peptide 1 (GLP-1), which promotes insulin secretion in the pancreas to improve insulin sensitivity. TGR5 signaling also promotes adipose tissue browning and energy metabolism to reduce weight.¹

The global epidemic of obesity and type 2 diabetes (T2D) has contributed to the increased prevalence of NAFLD, which is about 25% of the adult population in the world. NAFLD is a spectrum of chronic liver diseases ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) fibrosis and cirrhosis. NAFLD has surpassed viral hepatitis as the leading cause of hepatocellular carcinoma and liver transplant.³ Dysregulation of bile acid metabolism contributes to dyslipidemia, hyperglycemia, and insulin resistance in T2D.⁴ The gut-to-liver axis plays a critical

role in determining circulating bile acid pool size and bile acid composition, which control gut bacteria overgrowth. Obesity, T2D, and NASH fibrosis are associated with an altered gut microbiome. Bariatric surgery alters the gut microbiome to increase serum bile acids, FGF19, and GLP-1, and contributes to rapidly improved insulin sensitivity and glycemic control in overly obese patients.⁵

In inborn errors of bile acid synthesis, accumulation of toxic bile acid intermediates cause neonatal cholestasis, fibrosis, and hepatitis.¹ Obstruction of bile flow by stones, tumors, or inflammation of the intrahepatic small bile duct or extrahepatic common bile duct increases toxic bile acids and intermediates in the liver, leading to cholestatic liver injury and fibrosis. Progressive familial intrahepatic cholestasis (PFIC) is a collection of cholestatic liver diseases

TABLE 1. CHOLESTATIC LIVER DISEASES

PFIC	Mutations of bile acid transporters (BSEP, ABCB11), phospholipid transporters (ATP8B1, MDR3), FXR, TJP2, or MYO5B
PBC	Autoimmune destruction of the small bile ducts, portal infiltration, and fibrosis
PSC	Injury and fibrosis of both intrahepatic and extrahepatic bile ducts, biliary strictures, and obstructed bile flow
ICP	Reversible and typically resolves after delivery

TABLE 2. BILE ACID–BASED THERAPIES

Bile acids

- CA (Cholbam) and CDCA (Chenodiol): treat inborn errors of bile acid synthesis; gallstone dissolution
- UDCA (ursodiol [Actigall]): gallstone dissolution; reduces bile acid cytotoxicity
- NorUDCA: PSC

Bile acid sequestrants

- Cholestyramine, colesevelam: gallstone dissolution; reduces bile acid pool and stimulates bile acid synthesis; decreases FGF19; activates TGR5/GLP-1 and improves glycemic control; stimulates thermogenesis in brown adipose tissue

FXR agonists: anti-inflammation, cholestasis, NASH fibrosis, diabetes, obesity

- Obeticholic acid (OCA, OCALIVA): PBC
- Fexaramine (intestine-restricted FXR agonist): stimulates adipose tissue browning, stimulates GLP-1 secretion, improves insulin sensitivity, and reduces weight

FXR antagonists (intestine): PBC; reduces weight, improves diabetes

- Glycoursodeoxycholic acid, glycine- β -muricholic acid
- FGF19 analogue (NGM282): anti-inflammation and fibrosis; PSC, PBC, and NASH

of varying severity caused by deficiencies in bile formation and secretion. Mutations of BSEP (ABCB11), multidrug-resistant protein 3 (MDR3, ABCB4), FXR, tight junction protein 2 (TJP2), and myosin 5B (MYO5B) have been identified in patients with PFIC⁶ (Table 1). Primary biliary cirrhosis (PBC) involves autoimmune destruction of the small bile ducts, portal infiltration, and fibrosis with high prevalence in middle-aged women, whereas primary sclerosing cholangitis (PSC) causes fibrosis in bile ducts and obstruction of bile flow with higher prevalence in men. Intrahepatic cholestasis of pregnancy (ICP) is common in the third trimester of pregnancy.

Basic research in bile acid metabolism has been translated to bile acid–based therapies for cholestasis and NASH (Table 2). CA (Cholbam) and CDCA (Chenodiol) are used as bile acid replacement therapies for inborn errors of bile acid synthesis. Ursodeoxycholic acid (UDCA; ursodiol [Actigall]) has been used for gallstone dissolution. UDCA is used to treat PBC, whereas NorUDCA, a side-chain-shortened C23 UDCA homologue, is used to treat PSC.⁷ Bile acid sequestrants reduce the bile acid pool and result in CYP7A1 induction, increased bile acid synthesis, and reduced serum

cholesterol. Sequestrants also reduce FGF19 and stimulate TGR5-mediated GLP-1 secretion to improve insulin sensitivity and white adipose tissue browning.⁸ There is no approved drug therapy for NASH. Recently, obeticholic acid, a synthetic bile acid and potent FXR agonist, has been used for PBC treatment⁹ and is in phase III clinical trials for NASH fibrosis. NGM282, a nontumorigenic FGF19 analogue, has been used in clinical trials to treat PSC and PBC, and improves NASH fibrosis.¹⁰ However, bile acid–based drugs may have undesirable side effects such as pruritus, diarrhea, and hypercholesterolemia. It is anticipated that bile acid–based drug therapies will be approved for NASH treatment in the near future.

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