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Review Article

Bile acid metabolism and signaling in liver disease and therapy☆

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ABSTRACT

Bile acids play a critical role in the regulation of glucose, lipid, and energy metabolism through activation of the nuclear bile acid receptor farnesoid X receptor (FXR) and membrane G protein-coupled bile acid receptor-1 (Gpbar-1, aka TGR5). Agonist activation of FXR and TGR5 improves insulin and glucose sensitivity and stimulates energy metabolism to prevent diabetes, obesity, and non-alcoholic fatty liver disease (NAFLD). Bile acids have both pro- and anti-inflammatory actions through FXR and TGR5 in the intestine and liver. In the intestine, bile acids activate FXR and TGR5 to stimulate fibroblast growth factor 15 and glucagon-like peptide-1 secretion. FXR and TGR5 agonists may have therapeutic potential for treating liver-related metabolic diseases, such as diabetes and NAFLD.

1. Introduction

Bile acids are the end-products of cholesterol catabolism in the liver. Bile acids are physiological detergents important for emulsification of dietary fats, drugs, and lipid-soluble vitamins in the intestine and subsequent absorption and transport to the liver for metabolism and distribution to other tissues and organs. More recent studies have demonstrated that bile acids are signaling molecules that activate the nuclear receptor farnesoid X receptor (FXR) and G protein-coupled bile acid receptor-1 (Gpbar-1, aka TGR5) to regulate glucose, lipid, and energy metabolism. This review will discuss detailed bile acid synthesis and metabolism, regulation of bile acid synthesis, the roles of bile acid-activated nuclear receptors FXR and TGR5 in metabolic regulation, and bile acids as therapeutic drugs to treat liver diseases, diabetes, and obesity.

2. Bile acid metabolism

2.1. Bile acid synthesis in the liver

In human liver, two primary bile acids, cholic acid (CA) and chenodeoxycholic (CDCA), are synthesized from cholesterol through two pathways (Fig. 1).[1] The classic pathway is initiated by the rate-limiting enzyme cholesterol 7α-hydroxylase (CYP7A1). For CA (3α,7α,12α-trihydroxy-cholan-24-oic acid) synthesis, sterol 12α-hydroxylase (CYP8B1) is required for 12α-hydroxylation of 7α-hydroxy-4-cholesten-3-one, an intermediate and marker for the rate of bile acid synthesis. Mitochondrial steroid 27-hydroxylase (CYP27A1) catalyzes steroid side-chain oxidation, which is followed by oxidative cleavage of a 3-carbon-side-chain to form C24-bile acids, CA and CDCA. In the alternative pathway, CYP27A1 initiates bile acid synthesis by hydroxylation and oxidation of cholesterol to 3β-hydroxy-5-cholestenoic acid, which is then 7α-hydroxylated by oxysterol 7α-hydroxylase (CYP7B1) to form 3β,7α-dihydroxy-5-cholestenoic acid. These reactions also occur in the macrophages and steroidogenic tissues. It has been suggested that conversion of oxysterols formed in the macrophages to bile acids in the liver is a reverse cholesterol transport pathway for protection against atherosclerosis.[2] Bile acids synthesized in the liver are primary bile acids. Different primary bile acids are synthesized by various hydroxylases and epimerases, depending on species. In mouse liver, CDCA (3α,7α-dihydroxy-cholan-24-oic acid) is converted to α-muricholic acid (α-MCA, 3α, 6β, 7α), which is then epimerized to β-MCA (3α, 6β, 7β) and ω-MCA (3α, 6α, 7β) (Fig. 2A).[3] These MCAs are highly soluble. Mouse liver is capable of converting the secondary bile acid lithocholic acid (LCA, 3α) formed in the intestine to CDCA by 7α-hydroxylation. In humans and mice, some CDCA can be epimerized to ursodeoxycholic acid (UDCA, 3α,7β), a highly soluble bile acid. CDCA can be converted to hyocholic acid (3α, 6α, 7α) by 6α-hydroxylation. In mice, LCA can be hydroxylated to hyodeoxycholic acid (3α, 6α) and murideoxycholic acid (3α, 6β). Hyodeoxycholic acid can also be derived from MCA and hyocholic acid.[4] Bile acids form Na^{2+} salts and are conjugated to glycine or taurine by bile

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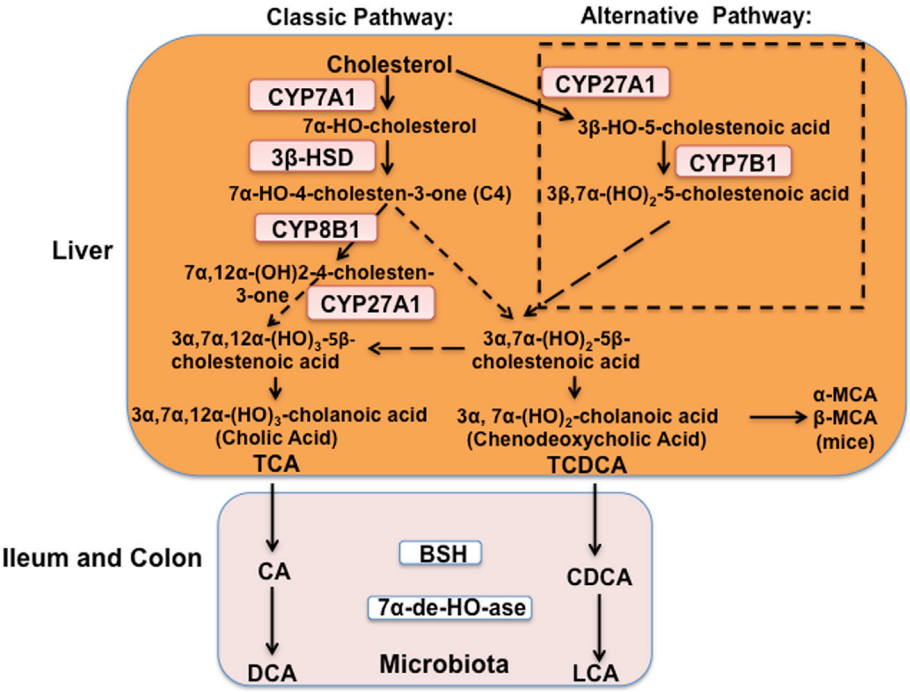

Fig. 1. Bile acid synthesis pathways. Two bile acid synthesis pathways are involved in the conversion of cholesterol to bile acids in the liver. The classic pathway is initiated by cholesterol 7α-hydroxylase (CYP7A1), and the alternative pathway is initiated by steroid 27-hydroxylase (CYP27A1). 3β-hydroxysteroid dehydrogenase (3β-HSD) converts 7α-hydroxycholesterol to 7α-hydroxy-4-cholesten-3-one (C4). Serum C4 level has been used as a marker for the rate of bile acid synthesis. Sterol 12-hydroxylase (CYP8B1) is a branch enzyme that synthesizes cholic acid (CA). Without 12α-hydroxylation, chenodeoxycholic acid (CDCA) is synthesized. Mitochondrial CYP27A1 catalyzes oxidation of the steroid side chain, and the peroxisomal β-oxidation reaction cleaves a 3C unit to form C24 cholestenoic acid, the backbone of most bile acids. CA and CDCA are the two primary bile acids synthesized in human liver. In mice, CDCA is converted to α- and β-muricholic acids (α-MCA and β-MCA, respectively). Bile acids are immediately conjugated to the amino acids taurine or glycine (TCA or TCDCA, respectively) for secretion into bile. In the ileum, TCA and TCDCA are deconjugated by bacterial bile salt hydrolase (BSH) activity, and the 7α-hydroxyl group is removed by bacterial 7α-dehydroxylase activity to form deoxycholic acid (DCA) and lithocholic acid (LCA), respectively. Bile acids (TCA, TDCA, TCDCA, Tα-MCA, and Tβ-MCA) are re-conjugated and circulated back to the liver. LCA is secreted into feces, and a small amount is circulated to the liver, conjugated to sulfite, and secreted into urine.

acid:Coenzyme A synthase and bile acid aminotransferase for secretion into bile via canalicular bile salt export peptide (Figs. 2B and 3). Glucuronidation of bile acids by UDP-glucuronosyltransferase also increases solubility for secretion of bile acids to bile via canalicular bile acid transporter multidrug resistance protein-related protein 2. Bile acids can also be sulfated by sulfotransferases to reduce toxicity and promote secretion into urine. Bile acids are stored in the gallbladder as mixed micelles with cholesterol and phosphatidylcholine. After a meal, bile acids are secreted into the intestinal tract to emulsify dietary fats, steroids, and lipid-soluble vitamins. In the intestine (colon), gut microbial bile salt hydrolases deconjugate conjugated-bile acids, and bacterial 7α-dehydroxylases convert the primary bile acids CA and CDCA to deoxycholic acid (3α, 7α) and LCA, respectively (Fig. 1). Most bile acids are re-conjugated to glycine or taurine, reabsorbed in the ileum, and transported back to the liver via the portal vein. The enterohepatic circulation (EHC) of bile acids recovers approximately 95% of bile acids (Fig. 3). In humans, the classic bile acid synthesis pathway is the predominant pathway (82%) for synthesis of a highly hydrophilic bile acid pool consisting of approximately 30% each of CA, CDCA, and deoxycholic acid. In contrast, in mice, the two pathways contribute equally to generate a highly hydrophilic bile acid pool containing approximately 50% CA and 50% α- and β-MCAs. In humans, bile acids are glycine- and taurine-conjugated at a ratio of 3 to 1, whereas in mice most bile acids (95%) are taurine-conjugated. The relative contribution of the classic and alternative bile acid synthesis pathways to bile acid synthesis determines the bile acid pool size and composition.

2.2. Regulation of bile acid synthesis

Regulation of bile acid synthesis is extremely complicated and not completely understood. The rate of bile acid synthesis, pool size, and composition varies by species and gender and is influenced by diet, circadian rhythms, hormones, drugs, the gut microbiota, pathological states, and genetic background. Bile acids maintain liver metabolic homeostasis and have anti-inflammatory properties under normal physiological conditions. Accumulation of high levels of hydrophobic bile acids in cholestasis causes liver inflammation and injury. Thus, bile acid concentrations have to be tightly regulated to maintain very low levels in the liver and blood circulation.

The EHC of bile acids from the intestine to the liver inhibits bile acid synthesis mainly by transcriptional repression of the rate-limiting enzyme CYP7A1 and the branch enzyme for cholic acid synthesis CYP8B1 (Fig. 3). The EHC of bile acids is highly efficient, occurs seven to eight times a day, and recycles approximately 95% of the bile acids in the pool. Two mechanisms of bile acid feedback regulation of bile acid synthesis have been suggested based on animal model studies (Fig. 3). In the liver, bile acids activate the nuclear receptor FXR to induce a negative nuclear receptor called small heterodimer partner (SHP). SHP inhibits *trans*-activating activity of hepatocyte nuclear factor 4 and liver-related homologue-1, which bind to the *Cyp7a1* and *Cyp8b1* gene promoters.[5] In FXR deficient mice, bile acid synthesis is upregulated and bile acids pool size is increased.[6] In SHP deficient mice, bile acid synthesis is still inhibited, suggesting other pathways may be involved in bile acid feedback

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