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REVIEW

Bile acids and sphingosine-1-phosphate receptor 2 in hepatic lipid metabolism

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Abstract The liver is the central organ involved in lipid metabolism. Dyslipidemia and its related disorders, including non-alcoholic fatty liver disease (NAFLD), obesity and other metabolic diseases, are of increasing public health concern due to their increasing prevalence in the population. Besides their well-characterized functions in cholesterol homoeostasis and nutrient absorption, bile acids are also important metabolic regulators and function as signaling hormones by activating specific nuclear receptors, G-protein coupled receptors, and multiple signaling pathways. Recent studies identified a new signaling pathway by which conjugated bile acids (CBA) activate the extracellular regulated protein kinases (ERK1/2) and protein kinase B (AKT) signaling pathway *via* sphingosine-1-phosphate receptor 2 (S1PR2). CBA-induced activation of S1PR2 is a key regulator of sphingosine kinase 2 (SphK2) and

Abbreviations: ABC, ATP-binding cassette; AKT/PKB, protein kinase B; BSEP/ABCB11, bile salt export protein; CA, cholic acid; CBA, conjugated bile acids; CDCA, chenodeoxycholic acid; CYP27A1, sterol 27-hydroxylase; CYP7A1, cholesterol 7α-hydroxylase; CYP7B1, oxysterol 7α-hydroxylase; CYP8B1, 12α-hydroxylase; DCA, deoxycholic acid; EGFR, epidermal growth factor receptor; ERK, extracellular regulated protein kinases; FGF15/19, fibroblast growth factor 15/19; FGFR, fibroblast growth factor receptor; FXR, farnesoid X receptor; G-6-Pase, glucose-6-phophatase; GPCR, G-protein coupled receptor; HDL, high density lipoprotein; HNF4α, hepatocyte nuclear factor-4α; IBAT, ileal sodium-dependent bile acid transporter; JNK1/2, c-Jun N-terminal kinase; LCA, lithocholic acid; LDL, low-density lipoprotein; LRH-1, liver-related homolog-1; M1–5, muscarinic receptor 1–5; MMP, matrix metalloproteinase; NAFLD, non-alcoholic fatty liver disease; NK, natural killer cells; NTCP, sodium taurocholate cotransporting polypeptide; PEPCK, PEP carboxykinse; PTX, pertussis toxin; S1P, sphingosine-1-phosphate; S1PR2, sphingosine-1-phosphate receptor 2; SHP, small heterodimer partner; SphK, sphingosine kinase; SPL, S1P lyase; Spns2, spinster homologue 2; SPPs, S1P phosphatases; SRC, proto-oncogene tyrosine-protein kinase; TCA, taurocholate; TGR5, G-protein-coupled bile acid receptor; TNFα, tumor necrosis factor α; VLDL, very-low-density lipoprotein

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hepatic gene expression. This review focuses on recent findings related to the role of bile acids/S1PR2-mediated signaling pathways in regulating hepatic lipid metabolism.

1. Introduction

Bile acids are synthesized from cholesterol and are known to solubilize cholesterol in the gallbladder and promote the digestion and absorption of dietary fats and fat-soluble vitamins (A, D, E and K) in the intestines. The production of bile acids is also known to be one of the predominant mechanisms for excretion of excess cholesterol from the body[1]. In addition to their beneficial effects, bile acids also produce toxic effects in the liver. It is becoming increasingly evident that bile acids exert various biological effects by activating different signaling pathways. However, the concept of bile acids acting as signaling molecules is recent. It was not until the past two decades that studies have reported that bile acids act as natural ligands for the farnesoid X receptor (FXRα)[2–4]. Following this discovery, bile acids have been shown to activate other nuclear receptors (pregnane X receptor, vitamin D receptor), G protein coupled receptors (GPCRs) (G-protein-coupled bile acid receptor 5 (TGR5), muscarinic receptor 2 (M2), sphingosine-1-phosphate receptor 2 (S1PR2)) and cellular signaling pathways (c-Jun N-terminal kinase (JNK1/2), protein kinase B (AKT), and extracellular regulated protein kinases (ERK1/2))[5,6]. Bile acids have also been implicated in the inflammatory response and various liver diseases, as well as the promotion of cancers such as colon cancer and cholangiocarcinoma[6–8]. The emerging role of bile acids as hormones and nutrient signaling molecules helped contribute to our understanding of glucose and lipid metabolism. In this review, we will discuss our current understanding of how bile acids and the S1PR2 regulate hepatic lipid metabolism.

2. Enterohepatic circulation of bile acids

Bile acids are synthesized from cholesterol in the hepatocytes and are actively transported into the bile duct system using ATP-binding cassette (ABC) transporter after conjugation with glycine or taurine. Hepatocytes secrete bile acids *via* bile salt export proteins (BSEP, ABCB11) along with phosphatidylcholine by ABCB4 and cholesterol by ABCG5/ABCG8[9,10]. As detergent molecules, bile acids keep cholesterol in solution within the gallbladder by forming micelles with cholesterol and phospholipids. The ratio of conjugated bile acids, cholesterol and phospholipids is highly regulated and excess cholesterol has been linked to an increased risk for cholesterol gallstone formation[11]. Bile is stored in the gallbladder and excreted into the duodenum in response to eating to activate pancreatic lipases and solubilize lipids to promote dietary fat absorption. Approximately 95% of bile acids are reabsorbed through the ileum by ileal sodium-dependent bile acid transporter (IBAT, SLC10A2)[12,13]. Bile acids reabsorbed from the intestines travel through the portal blood and return to the liver *via* the sodium taurocholate cotransporting polypeptide (NTCP, SLC10A1)[14]. A small portion of primary bile acids are converted into secondary bile acids by anaerobic gut bacteria, which can be either passively absorbed from the large intestine or secreted in the feces. During enterohepatic circulation, bile acids lost through fecal excretion must be replenished by *de novo* bile acid synthesis.

3. Bile acid synthesis

Bile acids are direct end-products of cholesterol catabolism. In humans, two primary bile acids, CA (3α, 7α, 12α-trihydroxy-cholanoic acid or cholic acid) and CDCA (3α, 7α-dihydroxy-cholanoic acid or chenodeoxycholic acid), are formed in the liver through two synthetic pathways, the neutral pathway and the acidic pathway (Fig. 1). The neutral pathway, also called the classic pathway, is the major pathway of generating bile acids for humans under physiological conditions and produces both CA and CDCA. The initiation of bile acid synthesis involves the enzyme cholesterol 7α-hydroxylase (CYP7A1) to catalyze the 7α-hydroxylation of cholesterol. In this rate-limiting step, *CYP7A1* gene expression is tightly regulated at the transcriptional level and by a negative feedback mechanism involving bile acids, glucagon, tumor necrosis factor α (TNFα) and fibroblast growth factor 15/19 (FGF15/19). In ileocytes, bile acids stimulate the production of FGF15/19 which can bind to the fibroblast growth factor receptor 4 (FGFR4)/β-Klotho complex on the cell membrane of hepatocytes and regulate bile acids and carbohydrate metabolism *via* activating several signaling cascades including JNK1/2 and ERK1/2[15–17]. Activation of the JNK1/2 pathway has been shown to repress *Cyp7a1* gene expression in hepatocytes[18]. *Fgfr4* and *β-Klotho* null mice have been shown to contain increased *Cyp7a1* mRNA levels and bile acid levels. These results demonstrate the critical role FGF15/19, an FXR target gene, plays in the regulation of CYP7A1 and bile acid synthesis. In addition, FXRα can induce the expression of an atypical orphan nuclear receptor, small heterodimer partner (SHP). SHP has no DNA-binding domain and functions as a common transcriptional repressor of nuclear receptors. SHP can form a heterodimer with several transcription factors, including hepatocyte nuclear factor 4α (HNF-4α) and liver-related homolog-1 (LRH-1), to inhibit their transactivation activities, which results in inhibiting *Cyp7a1* and sterol 12α-hydroxylase (*Cyp8b1*) transcription[19,20].

The acidic pathway is initiated by sterol 27-hydroxylase (CYP27A1) in the mitochondrial inner membrane and has been shown to be more active in cirrhosis and various liver diseases[21,22]. Since cholesterol concentration is very low in the inner mitochondrial membrane, the rate limiting step in acidic pathway may be the transport of cholesterol into the mitochondrion. The acidic pathway generates mostly CDCA. In addition to the liver, CYP27A1 is ubiquitously expressed in most tissues including the macrophages. CYP27A1 can catalyze cholesterol to form oxysterols by introducing a hydroxyl group to the carbon at either the 27 or 25 position in cholesterol[23–25]. The products, 27-hydroxycholesterol and 25-hydroxycholesterol, are known to be regulatory oxysterols that are important in maintaining cholesterol and fat levels in the liver[26].