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Review

Bile acids are nutrient signaling hormones

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ABSTRACT

Bile salts play crucial roles in allowing the gastrointestinal system to digest, transport and metabolize nutrients. They function as nutrient signaling hormones by activating specific nuclear receptors (FXR, PXR, Vitamin D) and G-protein coupled receptors [TGR5, sphingosine-1 phosphate receptor 2 (S1PR2), muscarinic receptors]. Bile acids and insulin appear to collaborate in regulating the metabolism of nutrients in the liver. They both activate the AKT and ERK1/2 signaling pathways. Bile acid induction of the FXR-α target gene, small heterodimer partner (SHP), is highly dependent on the activation PKCζ, a branch of the insulin signaling pathway. SHP is an important regulator of glucose and lipid metabolism in the liver. One might hypothesize that chronic low grade inflammation which is associated with insulin resistance, may inhibit bile acid signaling and disrupt lipid metabolism. The disruption of these signaling pathways may increase the risk of fatty liver and non-alcoholic fatty liver disease (NAFLD). Finally, conjugated bile acids appear to promote cholangiocarcinoma growth via the activation of S1PR2.

Contents

Abbreviations: ASBT, apical sodium dependent transporter; AKT, protein kinase B; BSEP, bile salt export protein (ABCB11); CA, cholic acid; CCA, cholangiocarcinoma; CDCA, chenodeoxycholic acid; CYP7A1, cholesterol 7α-hydroxylase; CYP7B1, oxysterol 7α-hydroxylase; CYP27A1, sterol 27-hydroxylase; CYP8B1, 12α-hydroxylase; DCA, deoxycholic acid; EGFR, epidermal growth factor receptor; ERK1/2, extracellular signal-regulated kinase; FGF15/19, fibroblast growth factor 15/19; FXR, farnesoid x receptor; G-6-Pase, glucose-6-phosphatase; GCA, glycocholic acid; GDCA, glycodeoxycholic acid; GPCR, G-protein coupled receptor; HNF4a, hepatocyte nuclear factor 4; LCA, lithocholic acid; LRH-1, liver-related homolog-1; LXR, liver X receptor; M1-5, muscarinic receptor 1-5; NAFLD, non-alcoholic fatty liver disease; NTCP, sodium taurocholate cotransporting polypeptide; P13K, phosphatidylinositol-3-kinase; PEPCK, PEP carboxykinse; PXR, pregnane X receptor; S1P, sphingosine 1-phosphate; S1PR2, sphingosine 1-phosphate receptor 2; SHP, small heterodimer partner; TCA, taurocholate.

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1. Introduction

In the past, bile salts were considered to be just detergent molecules that were required for the solubilization of cholesterol in the gall bladder, promoting the digestion of dietary lipids and stimulating the absorption of lipids, cholesterol and fat-soluble vitamins in the intestines [1]. Bile salts were also known to stimulate bile flow, promote cholesterol secretion from the liver, and have antibacterial properties. However, in 1999, three independent laboratories reported that bile acids were natural ligands for the farnesoid X receptor (FXR-α) [2–4]. The recognition that bile acids activated specific nuclear receptors started a renaissance in the field of bile acid research. Since 1999, bile acids have been reported to activate other nuclear receptors (pregnane X receptor, vitamin D receptor), G protein coupled receptors [TGR5, sphingosine-1-phosphate receptor 2 (S1PR2), muscarinic receptor 2 (M_2)] and cell signaling pathways (JNK1/2, AKT, and ERK1/2) [5,6]. Deoxycholic acid (DCA), a secondary bile acid, has also been reported to activate the epidermal growth factor receptor (EGFR) [7]. It is now clear that bile acids function as hormones or nutrient signaling molecules that help to regulate glucose, lipid, lipoprotein, and energy metabolism as well as inflammatory responses [5,6]. The role of bile acid-mediated signaling pathways in nonalcoholic fatty liver diseases has been discussed in several excellent reviews [8–12]. In this brief review, we will focus on how the insulin signaling pathway and FXR-α cross-talk to regulate hepatic nutrient metabolism.

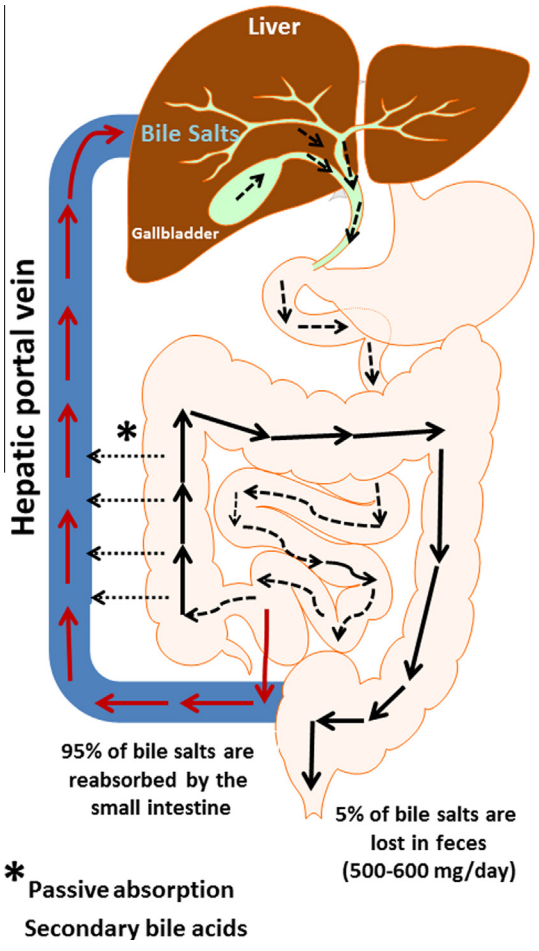

Fig. 1. Enterohepatic circulation of bile acids. Bile acids are synthesized and conjugated mainly to glycine or taurine in hepatocytes. Bile acids travel to the gall bladder for storage during the fasting state. During digestion, bile acids travel to the duodenum via the common bile duct. 95% of the bile acids delivered to the duodenum are absorbed back into blood within the ileum and circulate back to the liver through the portal vein. 5% of bile acids are lost in feces.

2. Enterohepatic circulation of bile acids

Bile acids are synthesized from cholesterol in liver hepatocytes, conjugated to either glycine or taurine and actively secreted via ABC transporters on the canalicular membrane into biliary bile. Conjugated bile acids are often referred to as bile salts. Bile acid synthesis represents a major output pathway of cholesterol from the body. Bile acids are actively secreted from hepatocytes via the bile salt export protein (BSEP, ABCB11) along with phospholipids by ABCB4 and cholesterol by ABCG5/ABCG8 in a fairly constant ratio under normal conditions [13,14]. Bile acids are detergent molecules and form mixed micelles with cholesterol and phospholipids, which help to keep cholesterol in solution in the gall bladder. Eating stimulates the gall bladder to contract, emptying its contents into the small intestines. Bile salts are crucial for the solubilization and absorption of cholesterol and lipids as well as lipid soluble vitamins (A, D, E, and K). They activate pancreatic enzymes and form mixed micelles with lipids in the small intestines, promoting their absorption. Bile acids are efficiently recovered from the intestines, primarily the ileum, by the apical sodium dependent transporter (ASBT). Bile acids are secreted from ileocytes, on the basolateral side, by the organic solute OSTα/OSTβ transporter [15]. Secondary bile acids, formed by 7α-dehydroxylation of primary bile acids by anaerobic gut bacteria, can be passively absorbed from the large bowel or secreted in the feces. Absorbed bile acids return to the liver via the portal blood where they are actively transported into hepatocytes primarily via the sodium taurocholate cotransporting polypeptide (NTCP, SLC10A1) [16]. Bile acids are again actively secreted from the hepatocytes into the bile, stimulating bile flow and the secretion of cholesterol and phospholipids. Bile acids undergo enterohepatic circulation several times each day (Fig. 1). During their enterohepatic circulation approximately 500–600 mg/day are lost via fecal excretion and must be replaced by new bile acid synthesis in the liver. The bile acid pool size is tightly regulated as excess bile acids can be highly toxic to mammalian cells.

3. Synthesis of primary and secondary bile acids

There are two pathways of bile acid synthesis in the liver, the neutral pathway and the acidic pathway (Fig. 2). The neutral pathway is believed to be the major pathway of bile acid synthesis in humans under normal physiological conditions. The neutral pathway is initiated by cholesterol 7α-hydroxylase (CYP7A1), which is the rate-limiting step in this biochemical pathway. CYP7A1 is a cytochrome P450 monooxygenase, and the gene encoding this enzyme is highly regulated by a feed-back repressive mechanism involving the FXR-dependent induction of fibroblast growth factor 15/19 (FGF15/19) by bile acids in the intestines. FGF15/19 binds to the fibroblast growth factor receptor 4 (FGFR4)/β-Klotho complex in hepatocytes activating both the JNK1/2 and ERK1/2 signaling cascades [17–19]. Activation of the JNK1/2 pathway has been reported to down-regulate CYP7A1 mRNA in hepatocytes [20]. FGFR4 and β-Klotho mice have increased levels of CYP7A1 and upregulated bile acid synthesis [21,22]. Moreover, treatment of FXR mice with a specific FXR agonist failed to repress CYP7A1 in the liver [23]. These results support an important role of FGF15, synthesized in the intestines by activation of FXR, in the regulation of CYP7A1 and bile acid synthesis in the liver. CYP7A1 has also been reported to be down-regulated by glucagon [24,25] and pro-inflammatory cytokines [15] and up-regulated by glucose and insulin during the postprandial period [26].