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REVIEW

Metabolic effects of intestinal absorption and enterohepatic cycling of bile acids

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Abstract The classical functions of bile acids include acting as detergents to facilitate the digestion and absorption of nutrients in the gut. In addition, bile acids also act as signaling molecules to regulate glucose homeostasis, lipid metabolism and energy expenditure. The signaling potential of bile acids in compartments such as the systemic circulation is regulated in part by an efficient enterohepatic circulation that functions to conserve and channel the pool of bile acids within the intestinal and hepatobiliary compartments. Changes in hepatobiliary and intestinal bile acid transport can alter the composition, size, and distribution of the bile acid pool. These alterations in turn can have significant effects on bile acid signaling and their downstream metabolic targets. This review discusses recent advances in our understanding of the inter-relationship between the enterohepatic cycling of bile acids and the metabolic consequences of signaling *via* bile acid-activated receptors, such as farnesoid X nuclear receptor (FXR) and the G-protein-coupled bile acid receptor (TGR5).

Abbreviations: ACCII, acetyl-CoA carboxylase 2; APO, apolipoproteins; ASBT, apical sodium-dependent bile acid transporter; BSEP, bile salt export pump; CYP7A1, cholesterol 7α-hydroxylase; DIO2, deiodinase 2; FAS, fatty acid synthase; FGF, fibroblast growth factor; FOXO1, forkhead box protein O1; FGFR4, fibroblast growth factor receptor 4; FXR, farnesoid X-receptor; G6Pase, glucose-6-phosphatase; GLP-1, glucagon-like polypeptide-1; HNF4α, hepatocyte nuclear factor 4 alpha; IBABP, ileal bile acid binding protein; LDL, low density lipoprotein; NTCP, Na^+-taurocholate transporting polypeptide; OATP, organic anion transporting polypeptide; OST, organic solute transporter; PEPCK, phosphoenolpyruvate carboxykinase; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; PPAR, peroxisome proliferator-activated receptor; SHP, small heterodimer partner; SREBP1c, sterol regulatory element binding protein-1c; T4, thyroid hormone; TGR5, G-protein-coupled bile acid receptor; VLDL, very low density lipoprotein

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1. Introduction

Research over the past 80 years has yielded considerable insight into the role of bile acids in intestinal fat absorption, hepatic bile formation, and cholesterol homeostasis[1]. However more recently, it has become apparent that bile acids also serve as signaling molecules with metabolic effects that extend beyond their control of hepatobiliary and intestinal function[1–3]. This has generated considerable renewed interest in bile acids and their metabolism. Bile acids are steroid acids synthesized from cholesterol in the liver[4]. Following their synthesis, bile acids are secreted along with other biliary constituents into the small intestine. After functioning in the proximal intestine to promote nutrient digestion and absorption, bile acids travel down the length of the small intestine to the terminal ileum for absorption. The bile acids are then carried in the portal circulation back to the liver for uptake and re-secretion into bile. The process of intestinal absorption is very efficient and about 95% of the bile acids secreted into the small intestine are reclaimed. Those bile acids that escape absorption pass into the colon and can be eliminated in the feces. Specialized membrane transporters expressed on the apical and basolateral membranes of the hepatocyte and ileal enterocyte largely mediate the movement of charged plasma membrane-impermeant bile acids molecules across those cell barriers[5]. For hepatocytes, the major transporters are the Na^+-taurocholate cotransporting polypeptide (NTCP; SLC10A1) and members of the organic anion transporting polypeptide (OATP) family (OATP1B1 and OATP1B3 in humans) on the sinusoidal membrane and the bile salt export pump (BSEP; ABCB11) on the canalicular membrane. For the ileal enterocyte, the major transporters are the apical sodium dependent bile acid transporter (ASBT; SLC10A2) on the brush border membrane and the heteromeric organic solute transporter alpha-beta (OSTα-OSTβ; SLC51A, SLC51B) on the basolateral membrane[6,7]. In this paradigm, the ASBT and OSTα-OSTβ function as major gatekeepers for the intestinal compartment of the enterohepatic circulation of bile acids. However, in addition to being important for determining the fate of bile acids, *i.e.*, their absorption *versus* their excretion in the feces, bile acid uptake by the ileal enterocyte is important for gut-liver signaling and regulation of bile acid synthesis. During transit through the ileal enterocyte, bile acids activate the nuclear receptor farnesoid X nuclear receptor (FXR), and increase transcription of the polypeptide hormone, fibroblast growth factor-19 (mouse ortholog, FGF15). FGF15/19 is then released from the intestine and travels to the liver where it signals through its cell surface receptor, a complex of the fibroblast growth factor receptor-4 (FGFR4) and its protein co-receptor β-Klotho, to repress transcription of the microsomal cytochrome P450 gene cholesterol 7α-hydroxylase (*Cyp7a1*) and inhibit hepatic bile acid synthesis[8]. Although a major function of the FXR-FGF15/19 pathway is to control hepatic bile acid synthesis and prevent bile acid accumulation, there is also evidence that this pathway can impact lipid, carbohydrate, and energy metabolism[9–11]. Bile acids are being viewed increasingly as metabolic regulators, and this has opened the door to targeting bile acid-related pathways as potential therapies for nonalcoholic fatty liver disease and other metabolic disorders[2,12,13]. This review focuses on the crosstalk between the enterohepatic cycling of bile acids and the metabolic consequences of signaling *via* bile acid-activated receptors such as FXR and TGR5 (the G-protein-coupled bile acid receptor) (Fig. 1).

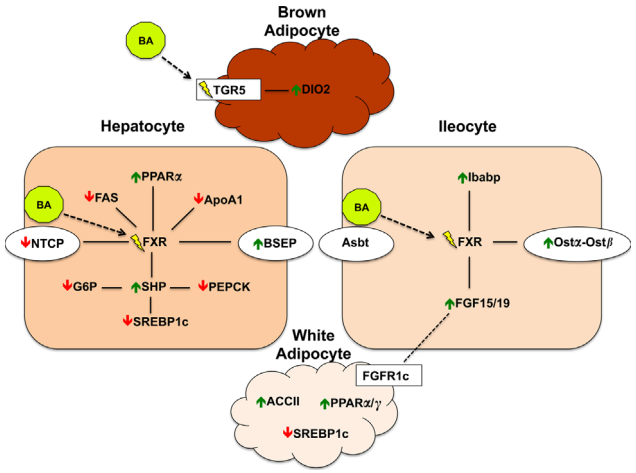

Figure 1 Bile acid (BA) mediated activation of FXR and TGR5 pathways in the enterohepatic circulation and systemic tissues. In the hepatocyte, bile acid activation of FXR increased SHP expression, which can decrease expression of SREBP1c and lipogenesis. Hepatic SHP activation can also lead to decreased expression of G6Pase and PEPCK, and reduced gluconeogenesis. FXR regulation of lipid metabolism and transport may involve decreasing the expression of fatty acid synthase (FAS) and apolipoproteins such as ApoAI, and inducting PPARα. FXR also controls bile acid transport by titrating the expression of NTCP (import) and BSEP (export) in the hepatocyte, and ASBT, OSTα-OSTβ, and IBABP in ileal enterocytes. FXR stimulation in the intestine increases the production of FGF15/19, which can have systemic effects on acetyl-CoA carboxylase 2 (ACCII), SREBP1c and PPAR expression in white adipose. TGR5 stimulation in the brown adipose (and skeletal muscle, not pictured) can stimulate deiodinase (DIO2) expression, which leads to increased energy expenditure and metabolic rate. TGR5 activation in the colon (not shown) can also increase release of glucagon-like polypeptide-1 (GLP-1), leading to improved glucose disposition and increased insulin sensitivity.

2. Bile acid signaling pathways and metabolic regulation

2.1. *Effects of hepatic FXR on metabolism*

FXR was established as the primary bile acid nuclear receptor in 1999[14,15]. Although expressed in a variety of tissues such as white adipose, kidney and adrenal, FXR is expressed at highest levels in the liver and intestine and is best known for its role in maintaining bile acid homeostasis. This is accomplished in part by regulating the expression of bile acid transporters such as BSEP, OSTα-OSTβ and NTCP, and the expression of transcription factors such as small heterodimer partner (SHP), which is involved in the repression of CYP7A1. However, FXR also regulates the metabolism of other lipids, either directly or indirectly *via* its effects on bile acid metabolism. For example, FXR-mediated repression of hepatic bile acid synthesis also reduces the catabolism and elimination of cholesterol as a result of the cholesterol-bile acid precursor-product relationship[4,16]. Through such direct or indirect mechanisms, FXR has been associated with a myriad of effects on lipid metabolism. With regard to triglyceride metabolism, activation of FXR by the natural agonist cholic acid reduces hepatic triglyceride levels by decreasing sterol regulatory element binding protein-1c (SREBP1c)-stimulated lipogenesis in a mechanism involving SHP[17]. These effects of FXR on SREBP1c expression and triglyceride synthesis may be mediated in part by the