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Bile acids as metabolic regulators

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Summary

Small molecule ligands that target to TGR5 and FXR have shown promise in treating various metabolic and inflammation-related human diseases. New insights into the mechanisms underlying the bariatric surgery and bile acid sequestrant treatment suggest that targeting the enterohepatic circulation to modulate gut-liver bile acid signaling, incretin production and microbiota represents a new strategy to treat obesity and type-2 diabetes.

Keywords

diabetes; bile acids; FGF15/19; incretin; microbiota

INTRODUCTION

Bile acids are physiological detergent molecules that facilitate the absorption of dietary lipids and vitamins in the gut (1). Studies in the past decades revealed that bile acids are signaling molecules that regulate lipid, glucose and energy metabolism. This regulatory function of bile acids is predominantly mediated by the bile acid-activated nuclear receptor farnesoid X receptor (FXR) and G protein coupled receptor TGR5, which is reviewed in details elsewhere (2). Emerging evidence suggests that bile acids in the small and large intestine regulate gut microbiota, incretin secretion and fibroblast growth factor 15/19 (FGF15/19) production, which modulate whole body lipid, glucose and energy homeostasis. In addition, recent findings revealed that the rapid improvement of glycemic control after gastric bypass surgery may be attributed to intestine bile acid signaling. This review focuses on the most recent findings that underscore the importance of the enterohepatic bile acid signaling in the regulation of metabolic homeostasis.

Regulation of bile acid synthesis by the gut-liver signaling axis

Bile acids are synthesized from cholesterol in the liver (2). As shown in Figure 1, cholesterol 7αhydroxylase (CYP7A1), a cytochrome P450 enzyme residing in the endoplasmic

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none

reticulum, catalyzes the first and rate-limiting step in the classic bile acid synthesis pathway. Newly synthesized bile acids are conjugated to amino acid glycine or taurine and are secreted across the apical membrane of the hepatocytes and stored in the gallbladder. A meal intake stimulates the release of bile acids into the intestinal tract to facilitate the absorption of dietary lipids and vitamins. Bile acids are efficiently reabsorbed in the ileum and transported back to the liver via portal circulation for re-secretion into the bile. The daily fecal loss of bile acids is only about 5%, which is replenished by de novo bile acid synthesis in the liver. The process of bile acid transport between the liver and the intestine is referred to as the enterohepatic circulation of the bile, which not only is important in nutrient absorption, but also plays a key role in regulating bile acid homeostasis and bile acid signaling.

Under normal conditions, the *CYP7A1* gene transcription, thus hepatic bile acid synthesis, is tightly regulated via bile acid-mediated negative feedback mechanisms in order to maintain a relatively constant bile acid pool (Figure 2). It is now clear that FXR plays a central role in mediating the negative feedback regulation of bile acid synthesis (2). In the hepatocytes, the bile acid/FXR/SHP (small heterodimer partner) cascade was first identified to inhibit *CYP7A1* gene transcription in response to elevated bile acids in the liver (3,4). In extra-hepatic tissues, FXR is highly expressed in the intestine that is also constantly exposed to high levels of bile acids. In 2005, Inagaki *et al.* revealed an intestinal FXR/FGF15/liver FGF receptor 4 (FGFR4) (human homolog: FGF19) signaling axis that links the gut bile acid sensing to the regulation of hepatic bile acid synthesis (5). The expression of FGF15 was detected at high levels in the ileum but presented at very low levels in other parts of the small intestine or colon, and was not expressed in mouse hepatocytes. Activation of intestine FXR by bile acids resulted in the transcriptional induction of FGF15. FGF15 then acts as an endocrine hormone to inhibit hepatic *CYP7A1* gene transcription via binding to the cell surface FGFR4 on hepatocytes. The FGF15/19-mediated gut to liver signaling has been demonstrated in *fgfr4* knockout mice (6,7), tissue-specific *fxr* knockout mice (8) and in human hepatocytes (9). More recently, Lan *et al.* showed that mice lacking the intestine basolateral bile acid efflux transporter *ostα* had significantly reduced bile acid pool size but also lower hepatic CYP7A1 gene expression (10), which was resulted from bile acid retention in the intestine that leads to FGF15 induction. The same group also demonstrated that mice lacking the intestine apical sodium dependent bile acid transporter (ASBT) showed reduced intestine FGF15 expression, higher hepatic CYP7A1 expression and resistance to atherosclerosis development (11). These studies reiterated the importance of gut-liver signaling axis in the regulation of bile acid and lipid homeostasis.

A positive feedback mechanism links gut microbiota to bile acid synthesis

Recent evidence suggests that the gut microbiota composition directly affects energy metabolism, leading to remarkable alterations of lipid, glucose and energy metabolism (12). The intestinal microbes generate short chain fatty acids from dietary carbohydrates that otherwise cannot be utilized as energy (13-15). The gut microbiota also affected the release of gut hormones such as glucagon like peptide 1 (GLP1) (16-19) and inflammatory mediators (20,21). Both macronutrients and bile acids can reshape the gut microbiota, which

in turn regulates the development of obesity and metabolic syndromes (22,23). Alterations of gut microbiota after bariatric surgery were also linked to weight loss (24-27).

It is well known that bile acids inhibit gut microbial growth through their detergent property and also FXR-dependent signaling mechanisms (28). On the other hand, gut bacteria also regulate bile acid biotransformation in the intestine, which alters bile acid composition (29). Germ-free rats and mice had increased bile acid synthesis and enlarged bile acid pool, and were resistant to diet-induced weight gain (30). More recent studies showed that in germ-free mice tauroconjugated bile acids, especially tauro-β-muricholic acid (T-βMCA), became predominant (31).

This is thought to be due to decreased bacterial bile salt hydrolase activity, which de-conjugates T-βMCA before it can be converted to secondary bile acids in the gut (Figure 1). A recent study in germ-free mice showed that despite an overall enlarged bile acid pool, increased muricholic acids acted as FXR antagonists and inhibited intestine FXR activity and FGF15 expression (Figure 2), which explains increased bile acid synthesis seen in germ-free mice (32). Same bile acid phenotypes can also be achieved by preventing cholic acid synthesis via *cyp8b1* knockout (33). Another study by Li *et al.* reported that treating mice with an antioxidant tempol, which has been shown to reduce body weight (34), resulted in two changes in mice (35). First, it caused a shift of the microbial community from Firmicutes towards Bacteroidetes, which is consistent with reduced short chain fatty acid production and weight loss. Second, decreased bile salt hydrolase activity from the Firmicutes resulted in T-βMCA accumulation, leading to enlarged bile acid pool. Importantly, bile acid composition critically determines the hydrophobicity of the bile acid pool, which affects both gut nutrient absorption and gut bile acid signaling. These recent studies underscore the important impact of bile acid composition on bile acid homeostasis and nutrient homeostasis.

SHP-2 is a key signaling component of the hepatic FGF15/19 signaling pathway

The intracellular signaling mechanisms that mediate FGF15/19 inhibition of *CYP7A1* gene in the hepatocytes are less well understood. FGFR4 is the predominant FGF receptor expressed in hepatocytes. The FGF15 signaling through FGFR4 requires another transmembrane protein called β-Klotho (36,37). A recent study by Li *et al.* identified the cytoplasmic tyrosine phosphatase SHP-2 as another key component in the FGF15/19 signaling in the hepatocytes (38). Hepatocyte-specific deletion of SHP2 resulted in increased hepatic expression of *CYP7A1* gene, hepatic bile acid accumulation and enlarged bile acid pool. On a chow diet, these mice developed liver injury consistent with bile acid damage to the hepatobiliary system. SHP-2 is a non-receptor tyrosine phosphatase with two Src-homology 2 (SH2) domains that allow its association with cell surface signaling components. SHP2 is required for activation of intracellular Ras/ERK pathway in response to mitogens and cytokines (39,40), which is consistent with ERK-dependent repression of *CYP7A1* by FGF19 (9). Other than direct binding to activated receptor tyrosine kinases, SHP2 can also be recruited to the cell surface signaling complex via interacting with adaptor proteins including the FGF receptor substrate 2 (FRS2). Interestingly, a recent report showed that FRS2 also plays a role in relaying FGF15 signaling and ablation of FSR2 in

hepatocytes abrogated FGF15/FGFR4 regulation of *CYP7A1* (41). It is well known that SHP2 regulates cell proliferation and tumorigenesis (39,42). Consistently, recent studies also suggested a role of FGF15 signaling in promoting liver regeneration in mice (43,44). A better understanding of the FGF15/19/FGFR4 signaling complex may facilitate the development of nontumorigenic variants of FGF19 for the treatment of human diseases (45).

Intestine Diet1 is a novel regulator of hepatic bile acid synthesis

About a decade ago, Mouzeyan *et al*. first reported that the *Diet1* locus confers protection against diet-induced hypercholesterolemia in the C57BL/6J (B6By) mouse sub-strain compared to the nearly genetically identical but atherosclerosis-prone C57BL/6J mouse strain (46). Further characterization revealed that the B6By strain showed elevated hepatic expression of CYP7A1 mRNA and enlarged bile acid pool, which likely conferred resistance to diet-induced hypercholesterolemia (47). In a recent report, the mutant gene that is responsible for increased hepatic bile acid synthesis in the B6By sub-strain was identified by genetic mapping and termed *Diet1* (48). This gene, encoding a 236 KDa protein, was shown to be expressed throughout the small intestine with relatively higher mRNA levels in the Ileum. Diet1 mRNA was not detected in the mouse liver, muscle or adipose tissues. It was noticed that the ileal FGF15 mRNA and protein was reduced in Diet1 deficient mice. In a human intestine cell line, Diet1 over-expression showed a modest effect on FGF19 mRNA. In contrast, Diet1 over-expression increased FGF19 protein secretion by ~3-fold. The function of Diet1 was not clear, but it shares sequence similarity to another protein Endotubin, which might be involved in intracellular protein trafficking (49). Interestingly, Diet1 was shown to interact with FGF19 and co-localize with FGF19 in an intracellular compartment distinct from endosomes/lysosomes in the intestine cell line. The identification of Diet1 that may control FGF15/19 secretion added a second layer of regulation of the FGF15/19 signaling axis in the intestine. Because the FGF15 protein has not been detected experimentally in mice so far, the investigation of the role of Diet1 on portal FGF15 levels was therefore limited. Further investigation of Diet1 function in hepatocyte-specific *fgfr4* knockout mice and analysis of genetic variations or mutations in *DIET1* gene in humans may shed more light on the role of Diet1 in the regulation of bile acid and cholesterol metabolism.

TGR5 mediates the bile acid sequestrant effect on glycemic control

It is well known that disruption of the gut-liver bile acid negative feedback signaling by bile acid sequestrants stimulates hepatic bile acid synthesis, which is effective in treating hypercholesterolemia in humans. Interestingly, adding colesevelam to statin therapy or other anti-diabetic drugs also improved glycemic control in type-2 diabetes mellitus (50-52). Until now the involvement of FXR in this glucose-lowering effect is still not certain given that hepatic and intestine FXR activity are likely either unchanged or decreased after sequestrant treatment (53). On the other hand, increased gut incretin GLP-1 may mediate the glucose-lowering effect of bile acid sequestrants (54). GLP-1, secreted from the ileal and colonic L-cells, enhances insulin secretion from the pancreatic β cells and inhibits glucagon production from the α cells (55). GLP-1 regulation of gastric emptying and satiety may also contribute to its effect on glycemic control (56,57). Macronutrients (dietary carbohydrates and fats) stimulate GLP-1 secretion in the gut. Activation of TGR5 by bile acid or TGR5 agonist

treatments also stimulated GLP-1 production in vitro and in vivo (58,59). However, whether endogenous bile acids, especially lithocholic acid, the most potent TGR5 ligand among all bile acid species, are able to activate TGR5 in the gut under normal physiology remains unclear. In this regard, two recent studies showed that bile acid sequestrants increased bile acid concentration in the distal ileum and colon where intestine L cells and TGR5 expression were highly enriched, which led to activation of TGR5 and GLP-1 secretion. Importantly, both studies showed that the bile acid sequestrantinduced GLP-1 secretion and glucose lowering were blunted in mice lacking TGR5 (60,61). An alternative proposed mechanism by which bile acid sequestrants increased GLP-1 production is that bile acid sequestrants interfere with dietary fat solubilization and absorption, which allows a higher concentration of dietary fatty acids to reach the distal ileum to induce GLP-1 secretion (62). In this case, the synergistic effect of dietary nutrients and bile acids on postprandial GLP-1 production will be enhanced by bile acid sequestrants.

Intestine bile acid signaling after bariatric surgery

A number of bariatric surgical procedures including the most common Roux-en-Y gastric bypass (RYGB) and the adjustable gastric banding (AGB) are being used as effective treatment for obesity and type-2 diabetes. Studies have shown that bariatric surgeries reduce food intake and increase satiety, and lead to gradual weight loss (63). However, significant improvement in glycemic control, β cell function and hepatic insulin resistance occurred even before weight loss (64). Extensive investigations into the mechanisms showed that post-surgery was associated with increased postprandial circulating gut hormones (Peptide YY, GLP-1), bile acids and FGF19 that correlated with improved glycemic control, weight loss and diabetic remission. Bariatric surgery promotes bile acids and undigested food to reach the distal intestine, which is thought to enhance incretin secretion. Elevated circulating FGF19 and bile acids can also lower postprandial blood glucose post-surgery, and these mechanisms would be dependent on FXR activation (65). In this regard, Ryan *et al.* compared the metabolic improvements after vertical sleeve gastrectomy (VSG) in wild type and whole body *fxr* knockout mice (27). Different from RYGB, VSG reduces gastric volume through ~70% removal of the stomach and does not involve the bypass of the proximal section of small intestine (66). They found that although VSG caused a sustained weight loss and improved glycemic control in wild type mice, FXR deficient mice regained weight at 8 weeks post-surgery and lost improved glycemic control. This is the first study to suggest a key role of FXR in mediating the effects of bariatric surgery. Unfortunately, changes in plasma bile acids and GLP-1 and intestine FGF15 levels post-surgery were not shown in this study, and whether the effect was mediated by intestine or liver FXR is not known. In addition, the result interpretation may be further complicated by the fact that *fxr* knockout mice already had lower body weight and enlarged bile acid pool size at the time of surgery, which may prevent further weight reduction post-surgery. It would be interesting to test the role of TGR5 in mediating the effects of bariatric surgery in a similar approach.

CONCLUSION

Research in the past two decades has unveiled important roles for bile acids in the regulation of hepatic lipid, glucose and energy metabolism. Small molecule ligands that target to TGR5

and FXR have shown promise in treating various metabolic and inflammation-related human diseases. New findings on the regulatory relationship between bile acid signaling, gut hormones and microbiota and energy balance are intriguing. Particularly, investigations into the mechanisms underlying the bariatric surgery and bile acid binding resin treatment suggest that modulation of the enterohepatic bile acid signaling represents a new strategy to treat obesity and type-2 diabetes. Changes in gut incretin production, bile acid signaling, hepatic CYP7A1 activity and gut microbiota likely contribute to the various metabolic benefits. It should also be kept in mind that the underlying mechanisms of these interactions are complex. Experimental outcomes may highly depend on the conditions and model systems used. Furthermore, the metabolic consequences of modulating enterohepatic bile acid metabolism could be very different in humans than in mice owing to the significant species difference in bile acid composition and metabolism.

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Key points

- A positive feedback mechanism links gut microbiota to hepatic bile acid synthesis through intestine FXR antagonism
- Diet1 is a novel regulator of intestine FGF19 secretion and controls hepatic bile acid and cholesterol homeostasis.
- The protein tyrosine phosphatase SHP2 is identified as a key signaling component in the FGF15/19 signaling regulation of CYP7A1 in the hepatocytes.
- Enhanced intestine FXR and TGR5 signaling contributes to the metabolic benefits of bariatric surgery and bile acid sequestrants.

Purpose of review

This review focuses on the latest understanding of the molecular mechanisms underlying the complex interactions between intestine and liver bile acid signaling, gut microbiota, and their impact on whole body lipid, glucose and energy metabolism.

Recent findings

Hepatic bile acid synthesis is tightly regulated by the bile acid negative feedback mechanisms. Modulating the enterohepatic bile acid signaling greatly impacts whole body metabolic homeostasis. Recently, a positive feedback mechanism through intestine FXR antagonism has been proposed to link gut microbiota to the regulation of bile acid composition and pool size. Two studies identified intestine Diet1 and hepatic SHP2 as novel regulators of CYP7A1 and bile acid synthesis through the gut-liver FXR/FGF15/19/FGFR4 signaling axis. New evidence suggests that enhancing bile acid signaling in the distal ileum and colon contributes to the metabolic benefits of bile acid sequestrants and bariatric surgery.

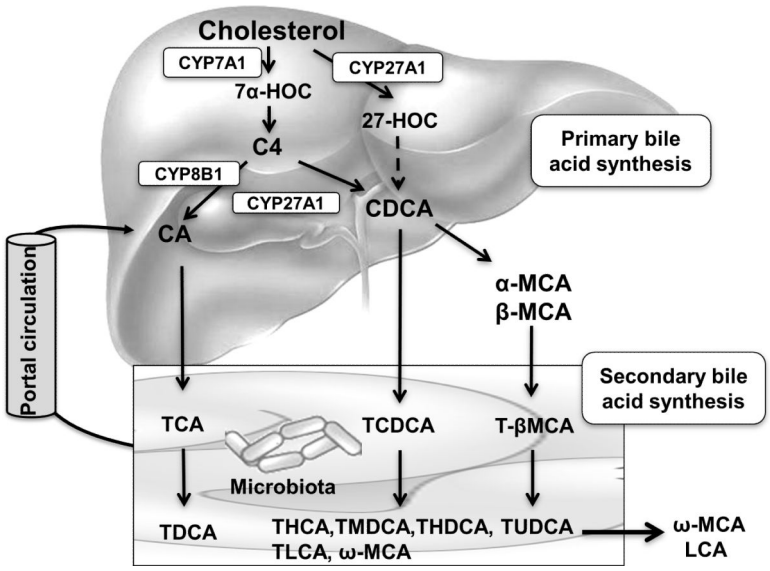

Figure 1. Bile acid biosynthetic pathways

Two major bile acid biosynthetic pathways are shown. The classic pathway is the major bile acid synthetic pathway in the liver. In this pathway, cholesterol is converted to 7α-hydroxycholesterol (7α-HOC) by the rate-limiting enzyme cholesterol 7α-hydroxylase (CYP7A1), which is located in the endoplasmic reticulum. The sterol 12α-hydroxylase (CYP8B1) converts the intermediate 7α-hydroxy-4 cholesten-3-one (C4) to 7α, 12α-dihydroxy-4- cholesten-3-one, leading to synthesis of cholic acid (CA). Without 12αhydroxylation by CYP8B1, C4 is eventually converted to chenodeoxycholic acid (CDCA). The mitochondrial sterol 27-hydroxylase (CYP27A1) catalyzes the steroid side-chain oxidation in both CA and CDCA synthesis. In the alternative pathway, CYP27A1 converts cholesterol to 27hydroxycholesterol (27-HOC), which eventually is converted to CDCA. In mouse liver, most CDCA is converted to α- and β-muricholic acid (MCA). MCA is only found in trace amount in humans. In the large intestine, bacterial 7-dehydroxylase removes a hydroxyl group from C-7 and converts CA to deoxycholic acid (DCA) and converts CDCA to lithocholic acid (LCA). CYP3A1 and epimerases also convert CDCA to the secondary bile acids, including hyocholic acid (HCA), murideoxycholic acid (MDCA), ω-muricholic acid (ω-MCA), hyodeoxycholic acid (HDCA) and ursodeoxycholic acid (UDCA). Most LCA and ω-MCA are excreted into feces.

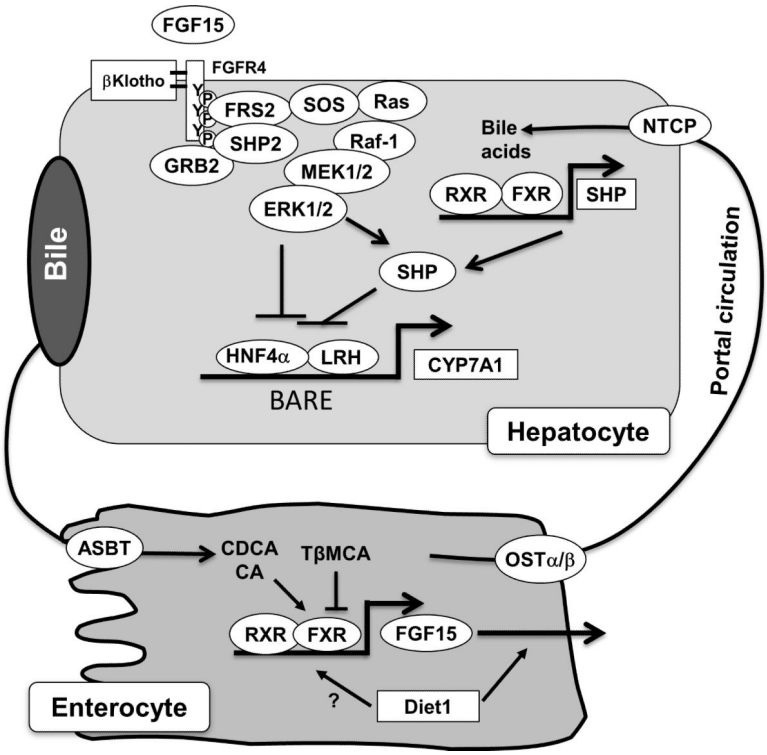

Figure 2. Mechanisms of bile acid feedback inhibition of bile acid synthesis

Bile acidactivated signaling inhibits CYP7A1 and therefore reduces hepatic bile acid synthesis. Nuclear receptors HNF4α and LRH1 bind to the bile acid response element (BARE) located in the CYP7A1 gene promoter and stimulate CYP7A1 gene transcription. In hepatocytes, bile acids activate FXR, which induces the repressor SHP. SHP interacts with and represses the transactivating action of HNF4α and LRH. In the intestine, bile acid-activated FXR induces the transcription of FGF15 (FGF19 in humans). Diet1 may promote FGF15/19 secretion from the intestine. Diet1 may also regulate FGF15 mRNA levels. FGF15/19 binds and activates FGFR4 on the hepatocytes. FGFR4 activates intracellular signaling pathways such as ERK, which leads to the repression of CYP7A1 gene transcription. SHP2 and FRS2 are identified as key components of the FGFR4 signaling complex that activates ERK1/2 in response to FGF15. The intracellular event downstream of ERK1/2 in CYP7A1 inhibition is less well understood, but may involve the inhibition of HNF4α or LRH. ERK has also been shown to stabilize SHP via direct phosphorylation. Disruption of the bile acid feedback signaling caused increased hepatic CYP7A1 expression and enlarged bile acid pool size.