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Journal Title: Acta Pharmaceutica Sinica B
Volume: Volume 5, Number 2
Publisher: Elsevier | 2015-03, Pages 129-134
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1016/j.apsb.2015.01.001
Permanent URL: https://pid.emory.edu/ark:/25593/r8pmv

Final published version: http://dx.doi.org/10.1016/j.apsb.2015.01.001

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Accessed August 9, 2023 8:19 AM EDT
Metabolic effects of intestinal absorption and enterohepatic cycling of bile acids

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Received 19 December 2014; received in revised form 30 December 2014; accepted 4 January 2015

KEY WORDS
Bile acids; Liver; Intestine; Transporters; Lipid metabolism; Energy homeostasis

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).

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\textit{Abbreviations:} ACCII, acetyl-CoA carboxylase 2; APO, apolipoproteins; ASBT, apical sodium-dependent bile acid transporter; BSEP, bile salt export pump; CYP7A1, cholesterol 7a-hydroxylase; DIO2, deiodinase 2; FAS, fatty acid synthase; FGF, fibroblast growth factor; FOXO1, forkhead box protein O1; FGRF4, fibroblast growth factor receptor 4; FXR, farnesoid X receptor; G6Pase, glucose-6-phosphatase; GLP-1, glucagon-like polypeptide-1; HNF4\textsubscript{a}, hepatocyte nuclear factor 4 alpha; IBABP, ileal bile acid binding protein; LDL, low density lipoprotein; NTCP, Na\textsuperscript{+}-taurocholate transporting polypeptide; OATP, organic anion transporting polypeptide; OST, organic solute transporter; PEPCK, phosphoenolpyruvate carboxykinase; PGC1\textsubscript{a}, 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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Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

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http://dx.doi.org/10.1016/j.apsb.2015.01.001
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. 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. This has generated considerable renewed interest in bile acids and their metabolism. Bile acids are steroid acids synthesized from cholesterol in the liver. 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. 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 canicular 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 (OST\(\alpha\)-OST\(\beta\); SLC5A1, SLC5B1) on the basolateral membrane. In this paradigm, the ASBT and OST\(\alpha\)-OST\(\beta\) 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 transport 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 \(\beta\)-Klotho, to repress transcription of the microsomal cytochrome P450 gene cholesterol \(7\alpha\)-hydroxylase (Cyp7a1) and inhibit hepatic bile acid synthesis. 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. 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. 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).
peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1α)18. In humans, FXR can induce expression of the nuclear receptor peroxisome proliferator-activated receptor alpha (PPARα), a master regulator of fatty acid metabolism19. In this way, activation of FXR could lead to increased lipolysis, increased fatty acid oxidation, and decreased lipogenesis. FXR’s list of actions also encompasses effects on lipoprotein metabolism20. For example, studies have shown that FXR can affect plasma lipid transport by decreasing expression of the apolipoproteins (Apo) as ApoAI and ApoCII, and increasing ApoCIII; FXR also induces expression of the very low density lipoprotein (VLDL) receptor to contribute to lipoprotein clearance21,22.

In addition to its role in lipid metabolism, FXR may regulate glucose metabolism23,24. FXR induction of SHP expression can decrease expression of hepatocyte nuclear factor-4 alpha (HNF4α) targets such as the gluconeogenic genes glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK)25. This may be accomplished in part by FXR modulation of hepatic PGC1α to repress expression of these gluconeogenic genes26. Activation of FXR also stimulates expression of pyruvate dehydrogenase kinase, which may further suppress glycolysis and enhance fatty acid oxidation27. Finally, activation of Akt and effects on insulin secretion and signaling by FXR suggest that multiple pathways may be mediating its effects on glucose metabolism28.

2.2. Effects of intestinal FXR on metabolism

FXR activation in the intestine, specifically the ileum, has a major role in bile acid homeostasis. FXR regulates expression of the ileal bile acid transporters, ASBT, OSTα-OSTβ, and the cytosolic ileal bile acid binding protein IBABP (FABP6)3. However in addition to control of bile acid flux and systemic exposure to bile acids, intestinally expressed FXR may affect metabolism via regulation of FGF15/19 production. Evidence indicates that the actions of FGF15/19 extend beyond its effects on bile acid metabolism, and include regulation of lipid and glucose metabolism11. For example, transgenic overexpression of FGF19 or treatment with recombinant FGF19 reduces adiposity and increases metabolic rate and levels of the satiety hormone leptin32. FGF19 has been shown to inhibit hepatic fatty acid synthesis by decreasing the expression of SREBP1c through indirect mechanisms33. It is also important to note that FGF19 can signal through FGF receptors in addition to FGFR4, and may act through these receptors in the central nervous system to alter lipid and glucose homeostasis34,35. Since many of these studies rely on use of exogenous recombinant FGF19, the question of whether these effects are physiological or pharmacological has been raised3. However, there is very strong genetic evidence from mouse models supporting endogenous FGF15’s ability to elicit similar metabolic effects36,37. These studies suggest that FGF15 acts in parallel with insulin to maintain normal glycogen levels by using an alternate Ras-ERK-p90RSK pathway38. In addition, FGF15/19 negatively regulates PGC1α and suppresses hepatic gluconeogenesis39. It has also been suggested that FGF15 may affect expression of forkhead box protein O1 (FOXO1), a regulator of gluconeogenesis40. Interestingly, Fgf4 deficiency or administration of FGFR4 antisense oligonucleotides improves hyperlipidemia, adiposity, and insulin resistance characteristic of fatty liver and diet-induced obesity, further supporting the hypothesis that FGF receptors in addition to FGFR4 are involved in the metabolic effects of FGF15/1940,41.

2.3. Effects of TGR5 on metabolism

TGR5 was identified as a bile acid-activated G-protein coupled receptor in 200342. With the growing appreciation of bile acids as signaling molecules, considerable study is being directed towards understanding the physiological functions of TGR543,44. For example, bile acid activation of TGR5 can regulate gallbladder filling, intestinal motility, and may have a role in bile acid-induced itch and the analgesia associated with cholestatic liver disease45,46. There are also metabolic effects associated with TGR5 signaling in brown adipose, muscle, and macrophages47. As with FXR, there is increasing interest in TGR5 as a potential therapeutic target for a variety of metabolic diseases12,13,47. For example, administration of the TGR5-selective synthetic agonist (INT-777) to mice attenuated diet-induced obesity and improved glucose tolerance48. The metabolic benefits may be due in part to increased metabolic rate and energy expenditure, secondary to TGR5-mediated increases in expression of deiodinase 2 (DIO2) and increased production of thyroid hormone (thyroxine, T4)49,50. These metabolic effects may also be mediated through bile acid activation of TGR5 on enteroendocrine L-cell in the distal small intestine and colon. In that mechanism, TGR5 signals to increase production and release of GLP-1, the incretin hormone that promotes insulin sensitivity, and thereby improves glucose disposition51,52. Therapies targeting GLP-1 are currently used to treat diabetes, and strategies that augment GLP-1 production, half-life, or activity may have benefit in other disorders such as hepatic steatosis and cardiac hypertrophy53. Finally, it should be noted that bile acids signal through other receptors and pathways in addition to FXR and TGR5, and additional research is needed to understand their contribution to the metabolic effects of bile acids3,43,54.

3. Metabolic effects associated with altered intestinal absorption of bile acids

3.1. Bile acid sequestrants and bile acid transporter inhibitors

Emerging research examining the effects bile acid sequestrants (bile acid binding resins) suggests a metabolic benefit associated with blocking intestinal absorption of bile acid beyond its well-characterized plasma cholesterol-lowering actions55. Bile acid sequestrants were originally used to treat hypercholesterolemia and bile acid malabsorption in the 1960s55,56. Disruption of the enterohepatic circulation of bile acids by blocking their intestinal absorption stimulates hepatic de novo bile acid synthesis from cholesterol. The hepatic demand for cholesterol is met by increasing hepatic cholesterol synthesis and plasma clearance of lipoproteins such as low density lipoprotein (LDL)57. Although not widely used to treat hypercholesterolemia after introduction of the HMG CoA reductase inhibitors (statins), bile acid sequestrants operating through this mechanism had shown benefit with regard to lowering plasma cholesterol levels and reducing cardiovascular disease in studies such as the Lipid Research Clinics Coronary Primary Prevention Trial58. However, in addition to their plasma cholesterol lowering properties, there is evidence that bile acid sequestrants can improve glycemic control, and the underlying mechanisms of action are being explored59,60,61. Various mechanisms have been thus far been implicated. Decreasing bile acid enterohepatic cycling will reduce the pool of bile acids available for micellar solubilization of lipids in the intestinal lumen, and is predicted to reduce lipid absorption in the proximal small intestine.
3.2. Knockout models of defective intestinal bile acid absorption

Although loss of either the ASBT or OSTα-OSTβ transporters impairs intestinal bile acid absorption, characterization of the Asbt and Ostα-Ostβ null mice is beginning to reveal important phenotypic differences in bile acid homeostasis that could affect lipid and glucose metabolism. For the parameters examined to date, the Asbt null mice display a similar metabolic phenotype to that described for treatment with bile acid sequestrants or ASBT inhibitors. Inactivation of the ASBT increases hepatic CYP7A1 and also reduces SREBP1c, improving triglyceride metabolism. With induction of hepatic bile acid synthesis and an enhanced flux of bile acids into the colon, there is also the potential for increased activation of TGR5. The phenotype of the Ostα null model is more complicated. Bile acids are internalized by the ileocyte, but cannot exit the cell due to loss of Ostα. This leads to activation of the FXR-FGF15/19 pathway and subsequent repression of CYP7A1 expression and a decrease in bile acid synthesis.

Figure 2 Predicted regulatory and metabolic effects of blocking ileal apical membrane (Asbt null mice) versus ileal basolateral membrane (Ostα null mice) bile acid transport. The arrows indicate the direction of predicted changes in Asbt null mice or Ostα null mice relative to wild type mice for the indicated physiological processes or pathways.

Indeed, treatment with a bile acid sequestrant has been shown to increase the incorporation of sterols and fatty acids into bile and feces, and alter lipid metabolism through excretion. In addition, by blocking the apical uptake of bile acid into the ileal enterocyte, bile acid sequestrants block activation of the FXR-FGF15/19 pathway. This will increase hepatic CYP7A1 expression and bile acid synthesis, altering the composition of the bile acid pool. In mouse models treated with a bile acid sequestrant, it has been proposed that the increased synthesis of bile acids via the CYP7A1 pathway increases entry of natural TGR5 agonists (such as cholic acid and cholic acid derivatives) into the systemic circulation. This leads to increased energy expenditure in muscle and brown adipose tissue. Blocking intestinal absorption also increases the flux of bile acids into the colon and can increase the TGR5-mediated release of GLP-1, which would act to promote insulin sensitivity. Not surprising, administration of a small molecule inhibitor of the ASBT has effects similar to those described for treatment with bile acid sequestrants or ASBT inhibitors.

Acknowledgments

Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (NIH, No. R01DK047987). The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH. Courtney B. Ferrebee was supported by a Research Supplement to Promote Diversity in Health Related Research from the NIH.

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