Metabolic Effects of Bile Acids: Potential Role in Bariatric Surgery

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SUMMARY

Although surgical treatment of obesity is becoming widely accepted, the mechanisms of how these operations mediate their beneficial effects remain elusive. Changes in bile acid handling after bariatric surgery hallmark these procedures and likely contribute to the efficacy of these metabolic operations. Establishing the crosstalk and intracellular signaling influenced by bile acids may lead to new insights into the pathogenesis and treatment for numerous diseases.

Bariatric surgery is the most effective and durable treatment for morbid obesity, with an unexplained yet beneficial side effect of restoring insulin sensitivity and improving glycemia, often before weight loss is observed. Among the many contributing mechanisms often cited, the altered handling of intestinal bile acids is of considerable therapeutic interest. Here, we review a growing body of literature examining the metabolic effects of bile acids ranging from their physical roles in dietary fat handling within the intestine to their functions as endocrine and paracrine hormones in potentiating responses to bariatric surgery. The roles of 2 important bile acid receptors, Takeda G-protein coupled receptor (also known as G-protein coupled bile acid receptor) and farnesoid X receptor, are highlighted as is downstream signaling through GLP-1 and its cognate receptor. Additional improvements in other phenotypes and potential contributions of commensal gut bacteria, such as Akkermansia muciniphila, which are manifest after Roux-en-Y gastric bypass and other emulations, such as gallbladder bile diversion to the ileum, are also discussed. (Cell Mol Gastroenterol Hepatol 2019;8:235–246; https://doi.org/10.1016/j.jcmgh.2019.04.014)

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Over the past 2 decades, bile acids (BAs) have gained a greater visibility and notoriety for their roles in regulating metabolism. Once only appreciated for their role in facilitating the availability of dietary fat,1 BAs are now known to exert hormonal functions throughout the body via nuclear and membrane receptors. Here, we review the expansive list of BA-sensitive signaling pathways, with a focus on intestinal and liver metabolism as regulated by BA availability. We aim to highlight the mechanisms by which BA signaling networks modulate complex physiologic events and explore potential opportunities for BA manipulating interventions that might improve obesity or related disease, such as type 2 diabetes (T2D), hyperlipidemia, and nonalcoholic fatty liver disease.

Bile Acid Synthesis and Enterohepatic Circulation

BAs are physiologic surfactants and cell signaling molecules that are synthesized from a cholesterol precursor in the liver. BA synthesis is facilitated by 2 distinct enzymatic pathways. The classical pathway contributes approximately 75% of the total BA pool and is regulated by cholesterol 7α-hydroxylase.2 The alternate (acidic pathway) is responsible for the remaining, approximately 25% of BA synthesis and is regulated by sterol-27 hydroxylase.3 Chenodeoxycholic acid (CDCA) and cholic acid (CA) in humans, and α-muricholic acid (MCA), β-MCA in mice, are the 2 major primary BAs; they are conjugated to either taurine (in mice) or glycine (in humans) in the liver, before they are actively secreted into the canalicular space of the liver, where they are concentrated over 100-fold in the fasting state before being stored in the gallbladder (GB) and secreted in the duodenum after stimulation by food.4 Secondary BAs, such as lithocholic acid and deoxycholic acid, are formed through additional reactions including bile salt hydrolase and 7α-dehydroxylase present in commensal gut bacteria.5,6 These gut bacteria additionally oxidize, sulfonate, and dehydroxylate BAs to form a diverse array of other BA species that vary in structure, function, and hydrophobicity. Most of the BAs remain in the gut lumen until they reach the terminal ileum5 where uptake into the enterocyte occurs via the apical sodium-dependent BA transporter and basolateral transporters OSTα/β.7 BAs are then transported back to the liver via portal circulation where they are reabsorbed and then enter the portal circulation and are then reabsorbed and then enter.
hepatic portal circulation in a process repeated 8–10 times per day. In a 70-kg human the sum of dietary cholesterol intake (5 mg/day/kg) and cholesterol synthesis (10 mg/day/kg) is nearly equal to fecal neutral sterol (8 mg/day/kg) and fecal acidic sterol (7 mg/day/kg) secretion. In mice, cholesterol intake (30 mg/day/kg), cholesterol synthesis (160 mg/day/kg), and sterol excretion (60 mg/day/kg for neutral sterols and 50 mg/day/kg for acidic sterols) are considerably higher.4 BA malabsorption can cause congenital diarrhea, steatorrhea, and reduced plasma cholesterol levels. The eventual loss of BAs in feces serves as the primary mechanism for cholesterol excretion from the body.

Bile Acid Regulation of Dietary Fat Availability

Dietary fat in the Western diet accounts for nearly 40% of calories ingested per day, and most (~95%) of the dietary lipids is derived from triacylglycerol (TAG), approximately 5% from phospholipids and less than 0.5% from cholesteryl esters.5 BA concentrations in the intestine range from 10 mM in the duodenum to 2 mM in the ileum,9 and these salts (predominantly sodium and potassium in most of the body) play a vital role in intestinal fat absorption. It is noteworthy that conjugated BAs have lower pKa values than the unconjugated acids and are therefore more ionized and exhibit greater water solubility at alkaline pH of intestinal chyme. In response to a meal, cholecystokinin stimulates GB contraction releasing bile into the duodenum. Dietary fats (mainly TAG and phospholipids) in the intestinal lumen are solubilized into micelles through the coordinated actions of BAs and various lipases (lingual, gastric, and most importantly pancreatic lipases)11 at the TAG droplet-water interface.12 Dietary TAGs are hydrolyzed by intestinal lipases generating monoacylglycerols13 sensed by GPR119. Fatty acids are sensed by free fatty acid receptors 1–4, which are absorbed by passive diffusion and specific transporters, such as CD36, across the brush border of enterocytes.14 These products are re-esterified to diacylglycerols and TAGs before being assembled into apolipoprotein B-48-containing chylomicron particles used for export to peripheral tissues.14

In the intestine, TAG synthesis is thought to occur mainly through the monoacylglycerols pathway, where monoacylglycerol acyltransferase joins monoacylglycerols and fatty acid–coenzyme A to form diacylglycerols.15 Diacylglycerols and fatty acid–coenzyme A are covalently joined to form TAG through the actions of DGAT1 and DGAT2. Dgat1 and Dgat2 are highly expressed in mouse intestinal tissue,16 with DGAT2 predominating lipid processing.17 In humans, DGAT1 is the only highly expressed enzyme in the intestine, with DGAT2 being expressed mainly in the liver. The coordinated roles of Dgat1 and Dgat2 in intestinal TAG synthesis are not completely understood, but recent studies in mice with intestine-specific deletion of individual isoforms, Dgat1 (Dgat1<sup>im</sup>) or Dgat2 (Dgat2<sup>im</sup>), suggest different and nonredundant roles in regulating chylomicrons and cytoplasmic lipid droplets.18 The influence of BAs on the activity and/or localization of these enzymes is unknown; however, humans with DGAT1 deficiency exhibit BA diarrhea and may exhibit altered BA metabolism/composition,19 although fecal BA measurements have not yet been reported in these patients.

Bile Acid Receptors

In lean and fasted humans, plasma BA concentrations are very low and hence most receptors are not activated. However, in metabolic stress or in the postprandial period, BA levels increase and composition changes resulting in the activation of various membrane bound and nuclear receptors. The quintessential membrane-bound receptor is a G-protein coupled BA receptor 1 (GPBAR1; TGR5),20,21 which is involved with rapid and dose-dependent elevation of intracellular cAMP levels.20 The most prototypical nuclear receptor is farnesoid X receptor (FXR; also known as NR1H4)22; other nuclear receptors include vitamin D receptor (NR1H1),23 pregnane X receptor (NR1H2),24,25 and constitutive androstane receptor (HR1H3). Other receptors include muscarinic receptors,26 active voltage-receptors (BKCA), calcium and chloride channels27 tyrosine kinase coupled receptors, and phospholipases (NAPE-PLD).28 BAs species bind these receptors with varying affinities and with a multitude of pathophysiological and pharmacologic effects. It has also been shown that conjugated BAs also activate sphingosine-1-phosphate receptor 2 leading to activation of the ERK1/2 and AKT signaling pathways.29

TGR5

TGR5 (encoded by GPBAR1) is a BA receptor that is a key mediator of the nongenomic actions of BAs. TGR5 is not expressed in hepatocytes, but is localized to sinusoidal endothelial cells,20 monocytes,20 enteroendocrine cells,31,32 adipose tissue,21,33 smooth muscle,34 skeletal muscle,21 pancreas,35 and the central nervous system.36 BAs activate TGR5 with a potency order of lithocholic acid>deoxycholic acid>CDCA>CA. TGR5<sup>-/-</sup> mice have mildly reduced BA pools,37,38 impaired glucose tolerance,39 and amplified inflammatory responses to partial hepatectomy, CA-enriched feeding, or bile duct ligation injury.39 Through kinase signaling pathways, TGR5 activation stimulates GB filling,40 modulates energy expenditure,41 suppresses hepatic glycolenolysis, and reduces inflammation and inflammatory macrophage activation.20,41-45 TGR5 also maintains intestinal epithelial barrier integrity and maintains intestinal homeostasis.46

Farnesoid X receptor

FXR is a nuclear BA sensor critical in regulating BA synthesis and transport. The receptor also serves as a critical regulator of glucose, lipid, and amino acid metabolism.47,48 Such features make it an attractive therapeutic target for T2D, dyslipidemia, BA disorders (inflammatory bowel disease, cholangitis), and nonalcoholic fatty liver disease.49-51 FXR is expressed as 4 different isoforms in humans52 and mice.53 FXR isoforms α1-α2 differ in the function of the N-terminal activation function domain and in an alternative splicing event giving rise to a 4 amino acid insertion (methionine-tyrosine-threonine-glycine) between the DNA binding domain and the hinge domain that
connects the DNA binding domain with the ligand binding domain. In humans, FXR\(\beta\) is highly expressed in small and large intestine and kidney, whereas FXR\(\alpha\) is highly expressed in adrenal and liver.\(^{52}\) FXR subsequently heterodimerizes with RXR and binds to FXR responsive element motifs, namely IR-1, depending on pathophysiologic or metabolic state.

Access to the FXR nuclear receptor is facilitated by many BA transporters and by passive diffusion. Reciprocally, FXR controls absorption of BAs via apical and basolateral transporters in both the liver and the intestine\(^{65}\) and these are essential for the function of the enterohepatic circulation. When bound by BAs (6\(\alpha\)-ECDCA>CDCA>deoxycholic acid>CA>lithocholic acid relative potency),\(^{55,56}\) nuclear FXR changes conformation to release corepressors, recruit coactivators, and drive target gene transcription programs. Other bile secondary acids, such as ursodeoxycholate acid (UDCA), are antagonistic.\(^{57}\) In the liver induction of small nuclear FXR helps in intestinal growth\(^{76}\) and nutrient absorption.\(^{73}\) Patel et al\(^{73}\) showed that GLP-2R plays a role in increasing circulating GLP-1 and BA levels, but despite markedly elevated levels of GLP-2 after vertical sleeve gastrectomy in mice, GLP-2R does not seem to play a vital role in reducing weight loss and glycemia postoperatively.

In the liver, FXR activation not only reduces BA synthesis but also reduces the expression of several genes mediating free fatty acid synthesis, including sterol responsive element binding protein 1 c, thereby attenuating de novo lipogenesis.\(^{63,79,80}\) FXR also represses the expression of microsomal triglyceride transfer protein\(^{79}\) and apolipoprotein B,\(^{81}\) thereby blunting very-low-density lipoprotein secretion. Hypercholesterolemia is promoted through FXR-mediated inhibition of BA synthesis and the resulting accumulation of the cholesterol precursor.\(^{82}\) Furthermore, FXR increases the expression of apolipoprotein C-II and decreases the expression of apo C-III, increasing the activity of lipoprotein lipase and consequently reducing triglyceride uptake by peripheral tissues. Consistent with these observations, mice deficient in FXR exhibit increased plasma lipids and cholesterol and increased hepatic steatosis.\(^{83-86}\) Recent studies also demonstrate a central role for BA stimulation of FXR and the release of FGF15/19 in transintestinal cholesterol excretion by increasing the hydrophobicity of the BA pool stimulating cholesterol efflux through the sterol-exporting heterodimer adenosine triphosphate binding cassette subfamily G member 5/\(\alpha_8\).\(^{87}\)

Using ileal organoids, Goldspink et al\(^{76}\) discovered that there is an elevation of L-cell cAMP concentrations and increase in L-type Ca\(^{2+}\) currents when administering the BA taurodeoxycholic acid and TGR5 agonist GPBAR-A individually leading to increased secretion of GLP-1. Similar results were achieved with administration of large amounts TAK-875, a free fatty acid receptor 1 agonist. Administration of a combination of TAK-875 and GPBAR-A causes a synergistic increase in Ca\(^{2+}\) response along with a synergistic stimulation of GLP-1 secretion from L-cells. In human studies, cholecystokinin-induced GB emptying results in significant GLP-1 secretion, which is abrogated with the use colesvelam, a BA sequestrant.\(^{77}\) Conjugated BAs released in the ileocolonic region in obese patients causes a statistically significant increase in postprandial GLP-1.\(^{78}\) GLP-2 is another proglucagon polypeptide secreted by L-cells, which helps in intestinal growth\(^{76}\) and nutrient absorption.\(^{73}\) Patel et al\(^{73}\) showed that GLP-2R plays a role in increasing circulating GLP-1 and BA levels, but despite markedly elevated levels of GLP-2 after vertical sleeve gastrectomy in mice, GLP-2R does not seem to play a vital role in reducing weight loss and glycemia postoperatively.

Bile Acid Regulation of Metabolism

By examining loss-of-function and gain-of-function of TGR5, it was discovered that the TGR5 pathway is essential in glucose homeostasis.\(^{31}\) TGR5 stimulates cAMP synthesis and activation of the MAPK pathway induces secretion of glucagon-like polypeptide 1 (GLP-1).\(^{20,34,73}\) GLP-1 is a hormone that has been shown to promote satiety, optimize nutrient absorption, stimulate the secretion of insulin, and impede gastric emptying.\(^{72,73}\) Katsuma et al\(^{73}\) showed that BAs interact with TGR5 to stimulate the secretion of GLP-1 in a murine enteroendocrine cell line STC-1. The promotion of GLP-1 secretion caused by BAs via TGR5 is caused by accumulation of intracellular cAMP within the STC-1 cells. BAs stimulate the release of GLP-1 in a dose-dependent manner.\(^{74,75}\) In TGR5 knockout mice, there is no significant increase in secretion of GLP-1 when BAs are introduced suggesting that TGR5 is necessary for BAs to stimulate the release of GLP-1 from intestinal L-cells.\(^{75}\) TGR5 mediates the release of GLP-1 in L-cells through modulating mitochondrial oxidative phosphorylation, which Causes the closing and opening of \(K_{ATP}/Ca\(_{\text{v}}\) channels and changes in the ATP/ADP ratio.\(^{51}\)

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released in the fed state. FGF15/19 acts on the liver to decrease glycemia and increase glycogen synthesis through a mechanism involving inactivation of the transcription factor cAMP regulatory element binding protein and the blunted expression of peroxisome proliferator-activated receptor γ coactivator-1α. Studies in FXR+/− mice further suggest these actions may additionally be mediated by small heterodimer partner, a direct FXR target and glucagon-like peptide 1 receptor.

Metabolic Effects of Manipulating Intestinal Bile Acid Availability

Dyslipidemia is more than 2 times more prevalent with T2D than in people without. Although statins are among mainstay therapies for treating dyslipidemia, BA sequestrant therapy has long proven effective in reducing low-density lipoprotein levels and improving glycemic control. The sequestrant works by mechanisms that are additive to the actions of other glucose-lowering drugs, such as metformin. Inhibition of ileal BA uptake by resins and luminal exposure to perfused BAs increases L-cell secretion and improves glycemic control through TGR5-FGF15/19 and FXR-LXRα axes. To more selectively modulate FXR and minimize undesirable side effects, novel strategies have been taken to develop tissue-specific FXR agonists. The gut-restricted FXR agonist fexaramine increased thermogenesis, adipose tissue browning, and insulin sensitivity, and reduced weight gain. These beneficial effects were mediated by increased FGF15 production leading to alterations in BA composition.

Obeticholic acid is a semisynthetic FXR-agonist that in the liver inhibits BA synthesis and promotes BA efflux, inhibits inflammation, and reduces fibrosis. In enterocytes, obeticholic acid stimulates FGF-15/19 release and inhibits intestinal inflammation. Interestingly, antagonism of FXR also has metabolic benefits. Oral administration of the antioxidant tempol reduced Lactobacillus bile salt hydrolase activity leading to accumulation of T-β-MCA, an FXR antagonist. Obese, high-fat-diet fed mice treated with tempol exhibited reduced obesity and improved insulin resistance. Because T-β-MCA is rapidly metabolized by bacteria through the actions of bile salt hydrolase, a variant of this BA, glycine-β-MCA, was developed and tested. G-β-MCA was tested in high-fat-fed mice and revealed to be a potent intestinal FXR antagonist resulting in decreased serum ceramide levels blunting obesity, insulin resistance, and development of fatty liver. These observed metabolic improvements were associated with white adipose tissue being and increased energy expenditure and were solely caused by inhibition of FXR signaling in the intestine. Interestingly, intestine-specific Fxr-null mice were unresponsive to the beneficial effects of Gly-β-MCA. Collectively, these data suggest a complex interplay between BAs, gut bacteria, and intestinal BA receptor signaling. Further studies are needed to clarify tissue-specific BA signaling pathways and how such pathways can be modulated to achieve therapeutic effect.

Bariatric Surgery

Bariatric surgery is the most effective and durable treatment for class III or higher obesity (body mass index ≥35 kg/m²) with and without diabetes. Currently, the 2 most popular bariatric procedures are Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy, both effectively promote weight loss. These bariatric operations reduce satiety, alter food preference, and improve nutrient handing with the beneficial side effect of improving insulin sensitivity before significant weight loss; we attributed these improvements to caloric restriction. Data from our longitudinal study showed that the average weight loss in bariatric subjects undergoing RYGB was 10% at 1 month, 27% at 6 months, 34% at 1 year, 33% at 2 years, and 27% at 5 years.

RYGB remodels the digestive tract by interrupting the stomach forming a small and vertical-oriented gastric pouch (≤30 mL), with the upper pouch reanastomosed to jejunum; bowel continuity is restored by jejunoejunostomy (Figure 1). The newly created digestive tract bypasses a major portion of the stomach, the duodenum, and the proximal jejunum, leading to decreased food intake and nutrient absorption. Following RYGB bile and pancreatic secretions drain through the foregut and meet with chime in the mid to distal jejunum at the site of the newly created jejunoejunostomy, where bowel continuity is restored. Hallmark of bariatric procedures is a chronic elevation in systemic BAs. Although increases in serum BAs are evident in the fasted state, increases are most predominant in the early postprandial period, particularly after RYGB. We measured by liquid chromatography–mass spectrometry the plasma BAs in class III obese (body mass index ≥40 kg/m²), preoperatively and longitudinally up to 2 years after RYGB. We observed bimodal significant increases in total BAs 1 month and 2 years after surgery. These increases were consistent with improvements in glucose tolerance and insulin sensitivity. The early changes (at 1 month) were characterized by significant increases in the secondary BA, UCDA, and conjugates GUDCA and TUDCA, whereas the increases at 2 years were caused by significant increases in CA and CDCA. Several hypotheses have been put forth to explain these improvements. The foregut hypothesis suggests that exclusion of the upper small intestine prevents secretion of “inhibitory” signals that promote insulin resistance and formation of T2D. A second hypothesis proposes that enhanced glucose use in the Roux (alimentary) limb favorably alters whole-body glucose disposal. A third hypothesis implicates the hindgut in modulating intestinal sodium-glucose cotransport in mediating the improvement in glucose tolerance and insulin sensitivity. A fourth hypothesis implicates intestinal satiety factors, such as oleoylthanolamine and BAs acting on brain dopaminergic circuits to impart satiety. Recent evidence obtained by our group and others supports a central role for BAs in each of these hypotheses.
Patients who have undergone either laparoscopic RYGB or laparoscopic sleeve gastrectomy have a significant increase in the secretion of GLP-1 and PYY by 1 week postoperatively. Kohli et al. discovered that patients after RYGB have a positive correlation between the postprandial levels of BAs and GLP-1. The data generated by us and others show that both bariatric procedures, RYGB and vertical sleeve gastrectomy, are associated with enhanced delivery of BAs to distal segments of the small and large intestine, to the sites where BA-responsive enteroendocrine cells are enriched, thus eliciting amplified hormonal secretory responses. These include increased GLP-1, PYY, and FGF15/19 release, all of which have insulin-sensitizing effects in the liver and peripheral tissue (eg, skeletal muscle and adipose).

**Bile Diversion**

To understand the role of BAs, we developed a murine mouse model connecting the GB to specific segments of the small intestine (eg, duodenum vs mid- or distal-jejunum vs terminal ileum), without stomach or intestinal remodeling.
examined. These data also suggest that intraluminal nascent BAs play an important role in the metabolic improvements observed with RYGB, and that these improvements seem to be site specific in nature.

Although the role of bile and BAs on enterocyte TAG metabolism is relatively unknown, our recent studies in mice with GB-IL suggests that bile may interfere with fatty acid absorption in the terminal ileum. GB bile is rich in phospholipids and provides the main source of lipid for intestinal chylothoracic assembly and secretion into lymph. Because phospholipid biosynthesis is tightly coupled to production of cellular membranes and intestinal phospholipid synthesis is required for phospholipid monolayers in endoplasmic reticulum, Golgi and lipid droplet membranes, the lipid inclusions we observed in GB-IL ileocytes could have resulted from impaired phospholipid handling as well.

### Summary

Overall, metabolic benefits of altering intestinal BA availability include weight-dependent and weight-independent effects (Figure 2). Bile diversion increases circulating BAs and improves glucose tolerance without altering body weight. This improved glucose homeostasis is typically attributed to effects of weight loss when observed clinically, but our findings suggest the weight-independent effects of bariatric surgery on glucose metabolism are driven by BAs. These findings implicate BAs as novel therapeutics for obesity and T2D, and adjuvant therapies in poor responders to bariatric surgery. With the continued development and greater availability of low-cost, high-throughput screening technologies for identifying risk and predicting response to therapy it may one day be routine to tailor bariatric procedures or suggest alternative, more effective procedures to those for whom it is warranted.

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