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Bile acids in glucose metabolism and insulin signalling — mechanisms and research needs

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Abstract

Of all the novel glucoregulatory molecules discovered in the past 20 years, bile acids (BAs) are notable for the fact that they were hiding in plain sight. BAs were well known for their requirement in dietary lipid absorption and biliary cholesterol secretion, due to their micelle-forming properties. However, it was not until 1999 that BAs were discovered to be endogenous ligands for the nuclear receptor FXR. Since that time, BAs have been shown to act through multiple receptors (PXR, VDR, TGR5 and S1PR2), as well as to have receptor-independent mechanisms (membrane dynamics, allosteric modulation of *N*-acyl phosphatidylethanolamine phospholipase D). We now also have an appreciation of the range of physiological, pathophysiological and therapeutic conditions in which endogenous BAs are altered, raising the possibility that BAs contribute to the effects of these conditions on glycaemia. In this Review, we highlight the mechanisms by which BAs regulate glucose homeostasis and the settings in which endogenous BAs are altered, and provide suggestions for future research.

Over the last 15 years, bile acids (BAs) have emerged as unexpected players in glucose homeostasis. In addition to their well-established role in promoting lipid absorption, BAs are also implicated in glucose metabolism and the secretion of glucoregulatory hormones[1]. In this Review, we highlight the mechanisms by which BAs influence glucose metabolism and suggest directions for future research.

BAs are cholesterol catabolites that are generated in hepatocytes (FIG. 1a). Following synthesis, BAs are conjugated to an amino acid and secreted into the bile. BAs are actively reabsorbed by enterocytes in the terminal ileum and travel via the portal vein to hepatocytes, where they are taken up and recycled. A proportion of BAs, however, escape ileal uptake, become modified by intestinal microorganisms, and are subsequently absorbed via passive diffusion in the colon[2]. Thus, BAs are found at high levels in the liver, bile and intestine

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(TABLE 1). Due to incomplete reuptake by hepatocytes, BAs are detected at low levels in plasma. The presence of BAs in the systemic circulation raises the possibility that BAs directly affect tissues throughout the body. High-affinity BA uptake transporters, however, are thought to be expressed predominantly in the liver and ileum[2–5]. Thus, it is unclear what concentrations of BAs could penetrate parenchymal cells or interstitial fluid in most tissues. The enterohepatic circulation of BAs has been reviewed extensively in REF.[3].

Numerous BA species are detectable in humans (FIG. 1b). They differ primarily in their hydroxylation sites and the presence or absence of a conjugated amino acid, predominantly glycine in humans. Of note, in rodents BAs are predominantly conjugated with taurine. In both humans and mice, a minor proportion of BAs also undergo sulfation[6,7]. BA modifications alter their physicochemical properties, including the so-called 'hydrophobicity' of a BA molecule[8,9]. It is worth noting that this descriptor is derived from the chromatographic separation method, whereby BAs are designated more hydrophobic if they are retained longer on a nonpolar chromatography column during elution with a polar solvent[9,10]. BAs are more accurately described as amphipathic, meaning they have a hydrophobic surface and a hydrophilic surface, and the number and position of hydroxyl groups on a BA molecule determine its amphipathic nature[10] (FIG. 1c). In addition to these physical descriptors, BAs can also be categorized as primary (synthesized in the liver) or secondary (generated by microbial modification of primary BAs in the gut[11]; FIG. 1). The composition of the BA pool is remodelled under numerous pathophysiological and experimental conditions[12–16] and this change in composition could influence BA function.

A unique feature of BAs is that they can act via multiple completely distinct molecular mechanisms, for example, by emulsifying lipids, by affecting cellular membranes, through allosteric effects and via receptor-mediated pathways[1]. Some of the mechanisms by which BAs act are known to have effects on glycaemia, and a number of other mechanisms have the potential to effect glycaemia[17,18]. In the first part of this Review, we describe these mechanisms, many of which were revealed by studies in preclinical models. In the second section, we discuss conditions that affect BAs and which might, in turn, affect glycaemia. Such conditions include insulin sensitivity, the microbiome and liver diseases. We also examine interventions and therapeutic agents that alter BA-dependent pathways, deliberately or unexpectedly. Finally, we highlight gaps in our knowledge and questions for future consideration.

Non-receptor-mediated mechanisms

The canonical physicochemical effect of BAs is to support the emulsification of water-insoluble lipids. It is possible that this process and other non-receptor-mediated BA effects could affect glycaemia, directly or indirectly.

Lipid emulsification.

Because of their amphipathic nature, BAs, in combination with polar phospholipids, are able to incorporate dietary lipids into mixed micellar solutions in the intestinal lumen. This micellization process increases the surface area of luminal lipids and improves the accessibility of intestinal lipases and the efficiency of fat hydrolysis[19]. This property of BAs

is essential to lipid absorption and total-body energy balance. Different BA species are differentially able to promote lipid absorption[20,21]. This ability to promote lipid absorption could be influenced by a BA's micelle-forming properties[8] and its permeability in the unstirred water layer lining the intestinal epithelium[22]. Evidence also suggests that enterocyte intracellular cholesterol esterification is regulated by BAs, although the mechanism of this is unknown[23].

Effects on cell membranes.

BAs can insert into cell membranes, including the plasma membrane, and impact membrane dynamics[24,25]. A 2014 study showed that this is the mechanism by which BAs activate the BA-sensitive ion channel whose physiological function remains elusive[26]. At supraphysiological doses, BAs can disrupt cell membranes and cause cell lysis[27–29]. For example, deoxycholic acid (DCA), a secondary BA produced by dehydroxylation of cholic acid (CA), is particularly potent, and an injectable synthetic form of DCA has been developed that takes advantage of this attribute, and was approved by the FDA in 2016 for reduction of fat under the chin[30].

BAs might affect intracellular membranes as well. DCA reportedly colocalizes with the mitochondrial outer membrane and perturbs its structure[31]. Tauroursodeoxycholic acid (TUDCA) has been reported to protect against endoplasmic reticulum (ER) stress, and treatment with TUDCA improves glycaemia in leptin-deficient *ob*/*ob* mice[32,33]. The molecular mechanisms by which TUDCA functions are not clear but could involve effects on the ER membrane itself.

Allosteric functions.

BAs can directly bind and modulate the activities of certain proteins. One notable example is *N*-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD), which is an enzyme found in the brain and intestine that converts membrane lipids into specialized bioactive lipids[34]. Products of NAPE-PLD include arachidonoylethanolamide (anandamide) and oleoylethanolamide, the latter of which promotes GLP1 secretion and both of which are involved in food intake regulation[35]. While solving the crystal structure of NAPE-PLD, researchers unexpectedly found DCA within the hydrophobic substrate binding pocket[36]. Moreover, DCA was found to bind and stabilize the enzyme and enhance its enzymatic activity. Further studies have shown that lithocholic acid (LCA), chenodeoxycholic acid (CDCA) and DCA bind NAPE-PLD (K_D ~20, 25 and 43 μM, respectively)[37]. At sufficiently high concentrations, LCA inhibits NAPE-PLD, whereas CDCA and DCA activate it, but the physiological relevance of these effects, and any downstream effects on metabolism have not yet been investigated.

Receptor-mediated mechanisms

BAs activate several nuclear receptors and G protein-coupled receptors, with differing potencies (TABLE 2). Much of our understanding of the roles of BA receptors in glycaemia comes from experiments using genetically manipulated mouse models, as well as small-molecule agonists and antagonists. An important consideration for interpreting such studies

is that BAs regulate their own synthesis through a series of negative feedback loops that converge on the key enzymes CYP7A1 and CYP8B1 (REFS[3,38,39]). Therefore, experimentally manipulating BA receptors frequently alters BA levels and composition (FIG. 2), which in turn influences other BA-sensitive pathways. In this section we review the reported involvement of BA receptors in glucose homeostasis; published mechanisms are summarized in FIG. 3. Of note, the reliance on preclinical models for these studies is a limitation. Mechanistic data in humans might be facilitated by identifying and studying individuals carrying genetic variants and by additional studies using receptor agonists.

FXR.

The first BA-responsive receptor discovered[40–42], FXR, is highly expressed in the liver, intestine and kidneys. Its role in glucose homeostasis has been investigated in multiple studies[15,17,43–45]. Some studies in mice have shown beneficial effects of FXR activation[43,44], while others have shown beneficial effects of deleting or inhibiting FXR[17,18]. Contradictions in the results between studies could be due to differential effects in the liver versus the intestine, pharmacokinetics of agonists and/or antagonists, sex, age, diet and genetic background. It is also worth noting that nuclear receptor deletion, antagonism or absence of ligand are not necessarily equivalent, as endogenous nuclear receptors can have effects in the basal, unliganded state[46].

The evidence that FXR activity is beneficial for glycaemia arose from studies in mice with FXR deficiency, as well as mice that were given FXR agonists. On normal chow diet, *Fxr*$^{-/-}$ mice showed worse intraperitoneal glucose tolerance and lower glucose disposal during hyperinsulinaemic-euglycaemic clamp than wild-type mice[44,47,48]. Furthermore, treating *ob*/*ob* and *db*/*db* mice with the FXR agonist GW4064 consistently lowered glucose excursions during intraperitoneal glucose and insulin tolerance tests[44,47]. The gut-restricted FXR agonist fexaramine improved glycaemia and reduced diet-induced weight gain in mice[15,43]. The proposed mechanisms of FXR beneficial effects on glucose metabolism include: suppression of gluconeogenic genes, due to FXR activation of the transcriptional repressor SHP[48]; protection from skeletal muscle lipotoxicity, via FXR-dependent liver lipid metabolism[48]; reduced weight gain due to adipose tissue browning, downstream of FXR-dependent alterations in BA composition[43]; increased GLP1 and insulin secretion, due to shifts in gut bacteria composition, which increase the TGR5 agonist taurolithocholic acid (TLCA)[15]; and increased secretion of fibroblast growth factor 15 (FGF15) and/or FGF19, described in detail below.

Conversely, other studies have shown that FXR inhibition improves glycaemia. Whole-body *Fxr*$^{-/-}$ mice and mice that lack FXR only in the intestinal epithelium had improved oral glucose tolerance, and this phenotype was frequently associated with reduced body weight[17,18,49–51]. Compared with vehicle-treated animals, when challenged with a high-fat diet, GW4064-treated mice displayed exacerbated weight gain, increased fasting glucose and insulin levels, and worsened glucose and insulin tolerance[45]. Furthermore, mice treated with glycine-β-muricholic acid (MCA) to antagonize FXR activity showed improved insulin tolerance and oral glucose tolerance and reduced fasting insulin levels compared with vehicle-treated control mice[1].

The proposed mechanisms for the beneficial effects of FXR inhibition include: decreased hepatic gluconeogenesis due to decreased pyruvate carboxylase activity (this has been suggested to be downstream of lower FXR-dependent intestinal production of hepatotoxic serum ceramides)[50]; reduced weight gain due to increased thermogenesis (also downstream of FXR-dependent production of serum ceramides)[17]; release of FXR-dependent suppression of proglucagon, the GLP1 precursor, that leads to increases in glucose-stimulated GLP1 release[51]; delayed intestinal glucose absorption due to increased glucose phosphorylation in enterocytes[49]; and release of FXR-dependent suppression of hepatic glycolytic genes[52].

FGF15 and/or FGF19.

By activating FXR, BAs induce robust transcription of the peptide hormone FGF15 and its human orthologue FGF19. FGF15 and/or FGF19, which are highly expressed in ileal enterocytes, have a key endocrine role in suppressing hepatic BA synthesis, which occurs through the FGFR4–β-Klotho receptor complex[53]. FGF15 and/or FGF19 are also important for maintaining normoglycaemia, as evidenced by the impaired glucose tolerance in *Fgf15*$^{-/-}$ mice and glycaemic improvements after transgenic expression or injection of FGF19[54–57]. The beneficial effects of FGF15 and/or FGF19 are potentially due to: reduced hepatic gluconeogenesis, downstream of FGF15- and/or FGF19-dependent dephosphorylation of the gluconeogenic transcription factor CREB[56]; increased hepatic glycogen synthesis, due to FGF15-/FGF19-dependent activation of an ERK-GSK3α/β phosphorylation cascade[57]; reduced body weight and adiposity[54,58], due to increased metabolic rate by increasing β-Klotho-dependent sympathetic nerve activity in brown adipose tissue[58]; and increased insulin-independent peripheral glucose disposal[59], downstream of FGF15 and/or FGF19 induction of ERK signalling in hypothalamic neurons[58,60,61]. Plasma FGF19 levels are reportedly reduced in patients with obesity and/or type 2 diabetes mellitus[62–64] and are negatively correlated with BMI[65]. However, the endogenous functions of FGF19 have been called into question[66,67].

The therapeutic prospects for FGF19 are potentially limited by the association of high levels of FGF15 and/or FGF19 with increased hepatocellular carcinoma in mice and humans[68,69]. However, non-tumorigenic variants of FGF19 have been generated and are now in development for the treatment of liver diseases. Variants M70 and M52 have been shown to protect against fibrosis, steatohepatitis and cholestasis in mice, effects that are expected to be secondary to suppression of BA synthesis[70–72]. M70 is also capable of suppressing BA synthesis in humans[70] and in a phase II clinical trial, it markedly improved markers of liver damage, cholestasis and inflammation in patients with primary biliary cholangitis[73]. A phase II trial of M70 in patients with nonalcoholic steatohepatitis (NASH) is underway[74].

Vitamin D receptor.

Some BAs, namely LCA and 3-keto-LCA, can activate the nuclear vitamin D receptor (VDR); however, these BAs are poorly taken up into cells. Although micromolar levels of LCA can activate VDR (comparable to FXR activation by CDCA)[75], the active form of vitamin D, 1α,25-dihydroxyvitamin D_3, activates VDR at nanomolar concentrations, making LCA about 1,000 times less potent than vitamin D[76,77]. Therefore, high doses of

LCA are required to activate VDR in vivo, and activation occurs more strongly under conditions of vitamin D deficiency[78]. VDR has been reported to have a role in maintaining glycaemia, and this function could be carried out via effects in islets[79], macrophages[80] or endothelial cells[81]. However, few studies have specifically investigated the effects of LCA–VDR signalling on glucose homeostasis. In vitro studies suggest that the LCA derivative, LCA propionate, protects β cells against dedifferentiation[82]. Another LCA derivative, TLCA-3 sulfate, induces insulin resistance in cultured hepatocytes, although this was not specifically linked to VDR[83]. Whether physiological or pharmacological levels of LCA and its derivatives regulate glucose metabolism in vivo remains to be determined.

TGR5.

The most extensively studied G protein-coupled receptor for BAs, TGR5 (also known as GPBAR1), is expressed in a wide range of tissues[84,85]. Preclinical studies suggest that TGR5 has a protective role in glucose homeostasis. The most widely reported mechanism by which this occurs is by TGR5-mediated increases in GLP1 secretion, accompanied by increased insulin secretion[86–90]. Alternative mechanisms by which TGR5 may influence metabolism include C/EBPβ-dependent suppression of macrophage infiltration into white adipose tissue[91] and increased energy expenditure[92,93].

Conditions and treatments that affect BAs

Endogenous BAs are altered in multiple physiological, pathophysiological and therapeutic conditions, and it is possible that these alterations contribute to BA-driven glycaemic regulation[12,13,15,94,95] (FIG. 4). Investigating the effects of human conditions on BA pool size and composition is inherently challenging. Stable isotope kinetic studies are a gold-standard method for assessing the synthesis and turnover of BAs in vivo, but require specialized expertise and are typically limited to small sample sizes. For studying larger populations, accessible specimens include plasma and faeces, but neither is a perfect representation of the concentrations and compositions of BA pools present in the liver, gallbladder or small intestine, the primary residences of BAs in the body. Nonetheless, in this section we Review the published literature, keeping these caveats in mind.

Impaired insulin signalling.

The first data indicating that insulin signalling regulates BA production and composition were from rodent models. Compared with healthy control animals, rodent models of insulinopenia and hyperglycaemia have a larger total BA pool size and a larger percentage of the BA pool consists of 12α-hydroxylated BAs[96–98]. The same is true in mice lacking hepatic insulin receptors[99]. The effects of hepatic insulin signalling on BA synthesis and composition are thought to be transcriptionally determined[100]. Evidence suggests that the transcription factor FOXO1, which is inactivated by insulin signalling, mediates the effect of insulin on BA composition[101] (BOX 1).

Several studies have analysed plasma BAs and markers of BA synthesis and how they relate to insulin sensitivity in humans. Insulin resistance has been reported to be positively correlated with the levels of plasma BAs, especially primary BAs and/or 12α-hydroxylated

BAs[16,94,102]. Obesity is associated with increased BA synthesis[103–105], 12α-hydroxylation[103] and alterations in BA transport[12,103]. Patients with type 2 diabetes mellitus have been reported to have increased concentrations of taurine-conjugated BA species[106]. In addition, kinetic studies have shown increased synthesis of BAs, particularly CA, in patients with type 2 diabetes mellitus[107]. Thus, preclinical and human studies support the consensus that hepatic insulin resistance increases BA synthesis, and might also cause other alterations in BA composition, such as increased 12α-hydroxylation. The dual concepts that first, insulin resistance, obesity or diabetes mellitus influence BA concentration and composition and, second, that BA concentration and composition can influence energy metabolism, suggest the possibility of adaptive or maladaptive feedforward signals contributing to metabolic disease.

Bariatric surgery.

Since 2009, numerous studies have shown that BA concentrations in the systemic circulation are increased after Roux-en-Y gastric bypass, biliopancreatic diversion and possibly vertical sleeve gastrectomy, but not after adjustable gastric banding[108]. These findings have been recapitulated in animal models, including mice, rats and minipigs[108–111]. The mechanisms by which bariatric surgery cause increased circulating BA concentrations are not yet known, and could be different depending on the surgical procedure. Increased synthesis alone is not the explanation. BA synthesis is increased in patients after biliointestinal bypass and biliopancreatic diversion[112,113], potentially because these procedures limit BA signalling in the ileum, which would decrease FGF19-dependent suppression of BA synthesis. In patients who have undergone Roux-en-Y gastric bypass or sleeve gastrectomy, BA synthesis is decreased in the short term and later returns to the normal range[113–115]. In sum, following metabolic surgery, there are probably alterations in BA transport that cause increased circulating BA concentrations. Preclinical models have suggested that concentrations of BA uptake transporters are increased in the ileum[109] or decreased in the liver after surgery[110,111]. The effects of bariatric surgery on BA composition have not come to consensus, potentially because of differences in surgical procedures, differences between animals and humans, and environmental factors.

Whether or not alterations in BA levels are the cause of improved glycaemia after bariatric surgery is also still a matter of debate. Proposed mechanisms include BA-driven increases in the secretion of GLP1, insulin or FGF19 (REF.[108]). Some studies in humans have supported correlations between secretion of these hormones and the BA subtypes present in the plasma[116], although BAs present in the plasma are not necessarily representative of BAs present in the relevant tissues. Evidence supporting a role for BAs in metabolic improvements following bariatric surgery has come from mice deficient in BA receptors. Mice lacking FXR[117,118], the FXR target SHP[119] or TGR5 (REFS[120,121]) have all been found to show resistance to the metabolic benefits of bariatric surgery. However, potential caveats arise due to differences between these knockout mice and their wild-type controls before surgery. Moreover, some have argued that the timing of elevated BA levels does not coincide with improved glycaemia after surgery[115]. Mechanistic studies are required.

Liver diseases.

It has been known for over 60 years that liver diseases differentially affect BA concentrations, distribution and composition[122]. One area that has been extensively examined is intrahepatic cholestasis of pregnancy (ICP). ICP is characterized by impaired bile flow as a consequence of genetic variation in hepatic BA transporters and high concentrations of pregnancy hormone metabolites, which competitively bind and reduce the activity of BA transporters and FXR[123]. Reduced activities of FXR and hepatic BA transporters cause elevations in maternal circulating plasma BA concentrations and altered BA composition, with a large increase in the proportion of CA in the pool[124,125]. Fetal plasma BAs, which are generated by the fetal liver, are also altered in ICP — concentrations are higher and CA predominates[125]. ICP is associated with an increased risk of adverse fetal outcomes[123].

ICP is also associated with metabolic dysfunction. Compared with healthy pregnant women, women with ICP are more likely to have impaired glucose tolerance and gestational diabetes[95,126]. Babies born to women with the condition are more likely to be large for gestational age compared with babies born to healthy pregnant women[95,127]. Among children of women who were affected by ICP, adolescent boys show higher BMI and fasting insulin levels and girls show larger hip and waist girth than children of non-affected mothers[128]. Whether or not BAs are responsible for these effects is unclear. In mice, feeding pregnant dams a CA-rich diet results in offspring that are more susceptible to weight gain and glucose intolerance on a Western diet[128]. These findings suggest the possibility of in utero metabolic programming in response to BAs.

The development of nonalcoholic fatty liver disease (NAFLD) and NASH is strongly linked to insulin resistance and dysbiosis[129]. It has also been reported that in patients with NASH, liver tissue concentrations of BA are higher and composition is altered compared with disease-free control livers[130,131]. Plasma BA concentrations are also higher, with altered composition in patients with NASH compared with those in healthy control individuals[132–137]. BA concentrations have been found to be significantly higher in patients with NASH with and without type 2 diabetes mellitus than in controls[136]. Because patients with NAFLD and NASH are typically more obese and more insulin-resistant than control participants, Legry and colleagues compared patients with NASH and control participants matched for BMI and insulin resistance[16]. This analysis revealed that alterations in BA metabolism are associated with insulin resistance, rather than liver necroinflammation itself. These findings highlight the complex interactions among insulin resistance, BAs and NAFLD and NASH. Nonetheless, BA-dependent pathways are being vigorously investigated as targets for the treatment of NASH, and these have been reviewed extensively elsewhere[129,138].

Gut microbiome.

The metabolism of BAs by gut microorganisms is an important determinant of BA composition. A common modification is the removal of the amino acid moiety of conjugated primary BAs, such as glycocholic acid and glycochenodeoxycholic acid, to create unconjugated or free BAs, such as CA and CDCA (FIG. 1). This deconjugation reaction

depends on the action of bile salt hydrolases, which are expressed in a wide range of bacteria and archaea[139]. Unconjugated BAs can undergo dehydroxylation at the 7 position to form secondary BAs; for example, CA is converted to DCA and CDCA is converted to LCA. Other possible modifications include epimerization and oxidation[140]. Although these conversions occur primarily in the microorganism-abundant colon where there are no active BA uptake transporters, unconjugated and secondary BAs can be passively absorbed[3]. Once returned to hepatocytes, unconjugated primary and secondary BAs can be re-conjugated[3,141]. However, the human liver is not efficient at re-hydroxylating secondary BA species; this is evidenced by the substantial proportion (~30%) of the human BA pool made up of DCA and its conjugated forms[142–144] (FIG. 2).

Agents that alter the microbiome can modify the composition of the BA pool. Individuals treated for 7 days with the gram-positive bacteria-directed antibiotic vancomycin showed significant reductions in the concentrations of secondary BAs in the plasma and faeces[145]. This effect occurred in response to vancomycin, which markedly altered the faecal microbiota composition, but not in response to amoxicillin. Indeed, different antibiotics have distinct effects on the composition of the BA pool[146]. Although it is outside the scope of this Review, it is worth noting that BAs can also influence the microbiome. A particularly intriguing example of this is presented by *Clostridioides difficile*: certain BAs (12α-hydroxylated species) promote the germination of *C. difficile* spores, while some BAs (secondary species) suppress vegetative growth[147].

The consequences of bacteria-modified BAs on host metabolism are currently under investigation[148] and new methodological advances hold the promise of new ways to investigate this. In 2018, Yao and colleagues colonized gnotobiotic mice with isogenic bacterial strains with or without bile salt hydrolase and found that eliminating BA deconjugation capacity was sufficient to attenuate high-fat diet-induced weight gain[149]. Such approaches are likely to further refine the effect of the microbiome–BA–energy metabolism axis.

Therapeutic agents.

Interventions that target BAs or BA signalling pathways are currently in use or being developed for metabolic indications[150,151]. BA sequestrants block intestinal BA reabsorption, consequently increasing BA faecal excretion and causing compensatory increases in BA synthesis, which lowers plasma cholesterol[152,153]. BA sequestrants are now also known to improve glycaemia in patients with type 2 diabetes mellitus. A meta-analysis of 17 randomized controlled trials showed that BA sequestrants reduced HbA_{1c} by 0.55%[154]. The mechanisms by which BA sequestrants improve glycaemia remain under debate. One possibility is that these resins increase BA concentrations in the colon, thus activating BA-dependent secretion of GLP1 (REF.[155]), but this has not been confirmed in other studies[156–158]. One study has provided evidence that BA sequestrant actually *reduces* BA-induced GLP1 secretion[159]. Mechanistic studies suggest that TGR5 is localized on the basolateral membrane of enteroendocrine cells and thus BAs must be absorbed in order to activate it[160,161], and this would preclude TGR5 activation by sequestrant-bound BAs.

Another possibility is that sequestrants increase splanchnic glucose uptake and utilization[156], potentially due to lower FXR signalling in the intestine[49].

Another mechanism by which BA reabsorption from the intestine can be blocked is to inhibit the apical sodium-dependent bile acid transporter (ASBT), and ASBT inhibitors have been developed to lower LDL cholesterol[150,162,163]. Studies in rodent models of type 2 diabetes mellitus have suggested that, like BA sequestrants, ASBT inhibitors may also be able to improve glycaemia[164–166]. Consistent with this, inhibiting ASBT in patients with type 2 diabetes mellitus improves glycaemia[167,168]. In non-diabetic participants, ASBT inhibitors might increase GLP1, but do not affect plasma levels of glucose[169,170].

Obeticholic acid (OCA, INT-747) is an FXR agonist that is a leading candidate in clinical trials for the treatment of NASH. In a small study that included patients with type 2 diabetes mellitus, OCA improved insulin sensitivity in hyperinsulinaemic–euglycaemic clamps[171]. However, in a larger study, OCA increased fasting insulin and thus worsened insulin resistance, as calculated by the homeostasis model of assessment (HOMA)[172]. Further studies are required to determine the effects of OCA on glycaemia in humans. We note that in addition to its direct effects on FXR-dependent energy metabolism pathways, OCA (and any other agonist or antagonist of FXR) will also have major consequences on BA concentrations and composition, because of the potent, FXR-mediated negative feedback loops on CYP7A1 and CYP8B1, thus potentially influencing other BA-dependent pathways.

The BA TUDCA has long been used in the treatment of liver diseases, due to its ability to increase bile flow. Studies in rodents have suggested that TUDCA might also improve glycaemia, potentially through its effects on ER stress in metabolic tissues and/or β cells[33,173]. Indeed, in obese individuals treatment with TUDCA (1,750 mg/day) for 4 weeks resulted improved hepatic and muscle insulin sensitivity[174]. However, this treatment did not affect ER stress markers, and another study with the related unconjugated molecule ursodeoxycholic acid (UDCA; 20 mg per kg per day) actually induced some ER stress markers in the liver[175]. Thus the mechanisms involved in the activity of TUDCA and UDCA continue to be elusive.

Metformin is the most widely used anti-diabetes drug and numerous mechanisms of action have been proposed, including several implicating BAs. One possibility is that metformin impairs intestinal BA uptake[176,177], potentially increasing GLP1 secretion. Another study in humans has shown that metformin enhances BA-induced GLP1 secretion[178]. Metformin is known to activate AMPK, and it has been suggested that AMPK directly phosphorylates and inhibits FXR activity[179]. Other evidence indicates that metformin’s effect in altering the gut microbiome changes BA levels and/or composition, resulting in lower intestinal FXR activity[180,181].

Future research needs

To fill the gaps in our understanding of the mechanisms linking BAs with glycaemia, especially those of clinical relevance, several laboratory approaches are available. First, many rodent models of BA receptor activation and/or inhibition are associated with

alterations in BA composition (FIG. 2). Therefore, it is not possible to separate the direct effects of the receptor on glucose metabolism pathways per se from its indirect effects (via altered BA composition) on TGR5, or other receptor-mediated or non-receptor-mediated BA effects. One way to approach this concern is to use mice with controlled BA pools, such as those lacking the CYP2C family of enzymes, which generate the 6-hydroxylated MCAs[182]; those lacking CYP8B1, which generates 12α-hydroxylated BAs, and which is known to effect glycaemia via its effects on BA composition[13,183,184]; and those with designer microbiota reconstitution[149]. Second, lack of BA receptors or BA synthesis enzymes might engender long-term and compensatory phenotypes that make data interpretation challenging. Exemplifying this are the studies of bariatric surgery in BA receptor knockout mice, which have phenotypic differences from wild-type mice at baseline. Temporal control of genetic knockouts, using inducible systems, could temper these caveats.

Third, there are differences in BA composition between humans and mice (FIG. 2). Humans have predominantly glycine-conjugated BAs (compared with taurine in mice), abundance of DCA and conjugated forms (compared with rodents, which efficiently re-hydroxylate DCA into CA), and very low levels of MCAs (compared with high levels in mice and rats). One potential approach could be to use human liver chimeric mice, although these are known to retain a substantial proportion of murine hepatocytes. At a minimum, researchers should keep these differences in mind and consider comparing humanized versus murine BA pools where possible, such as in in vitro experiments. Fourth, there are differences in the primary structure of FXR between species that influence sensitivity to certain BA subtypes[185]. These differences call for using human cells when possible, and stem cell-derived organoid methods might provide novel experimental platforms. Finally, systems biology approaches might help resolve the complexity of the BA functionality network (FIG. 4). Ultimately, clinical and translational studies in human subjects will have the most impact in determining the mechanisms linking BAs with glucose metabolism.

Conclusions

BAs are unique in their ability to act as structural molecules, allosteric modulators and signalling molecules. It is through a combination of these mechanisms that BAs affect key aspects of metabolic homeostasis. Whether or not these are druggable targets in patients with type 2 diabetes mellitus is not yet clear. New opportunities and experimental tools will allow basic, translational and clinical researchers to answer this question.

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Key points

- Pathways in multiple tissues have been reported to link bile acids (BAs) with glycaemia.
- Physiological and disease settings, and several medications, influence BA levels and composition.
- When interpreting studies with genetic and pharmacological modulations of BA receptors, one should take into consideration that these modulations affect BA concentration, distribution and composition.
- Rodent models with humanized BA composition will increase the relevance of basic research findings to human health.
- Human cells and organoid models should be used to address the interspecies differences in BA receptor structure.

Box 1 |

Hepatic insulin signalling regulates bile acid pool composition in mice and humans

Evidence from mice

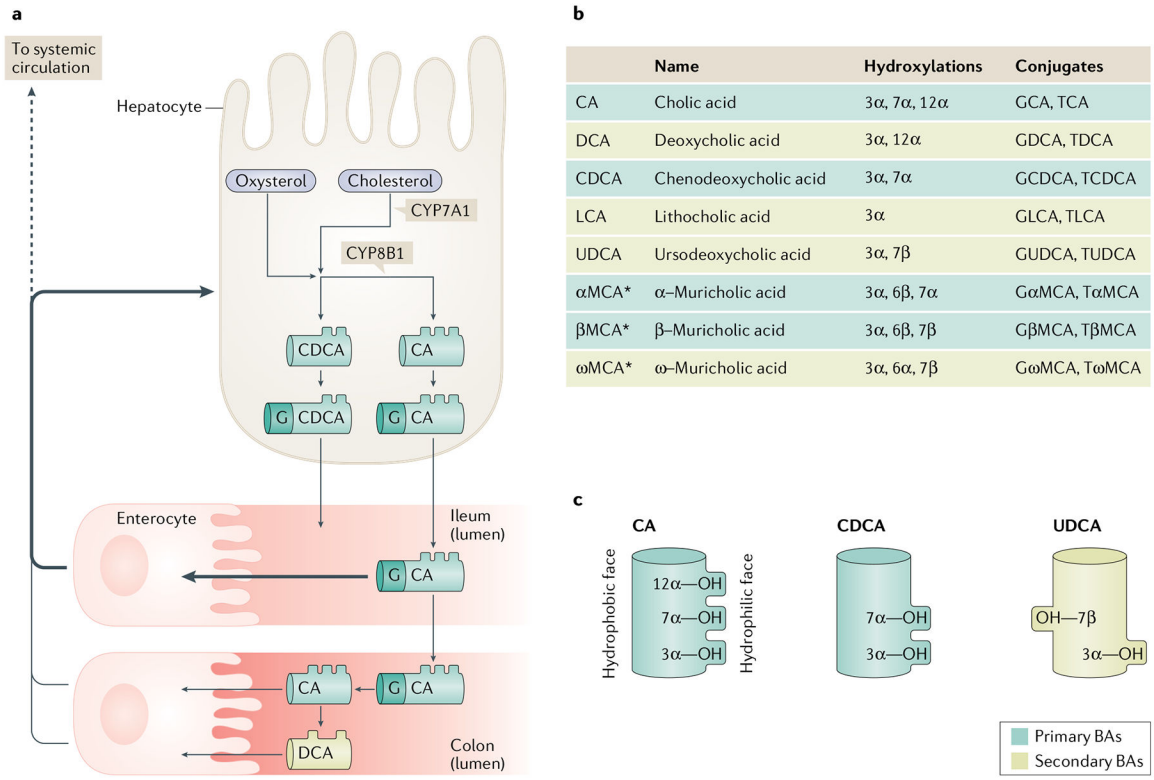
- The insulin-repressible forkhead box protein o (FOXO) transcription factors increase mRNA expression of the sterol 12α-hydroxylase, *Cyp8b1*, in mouse liver. Hepatic *FoxO1* ablation in mice reduces the levels of 12α-hydroxylated bile acids (BAs) in enterohepatic tissues[101]. Triple hepatic ablation of *FoxO1*, *FoxO3* and *FoxO4* exacerbates this phenotype [R.A.H., unpublished], demonstrating redundant functions of FOXO transcription factors on *Cyp8b1*.
- Mouse and rat models of hyperglycaemia and insulinopenia are surmised to have higher FOXO activity, and they show increased levels of 12α-hydroxylated BAs. These models include rodents treated with the β-cell toxins streptozotocin and alloxan and NOD mice[96–98,186]. mice lacking hepatic insulin receptors also show increased levels of 12α-hydroxylated BAs[101].

Evidence from humans

- Stable isotope kinetic studies have shown increased synthesis of cholic acid, the primary 12α-hydroxylated BA, in patients with type 2 diabetes mellitus compared with controls matched for BMI[107].
- In non-obese human volunteers, insulin resistance (as assessed by gold-standard hyperinsulinaemic–euglycaemic clamp studies) is associated with increased plasma levels of 12α-hydroxylated BAs[94].
- Individuals with insulin resistance and obesity have higher CYP8B1 activity compared with non-obese control individuals, as determined by plasma levels of the CYP8B1 product, 7α,12α-dihydroxy-4-cholesten-3-one[103].

Summary

These studies demonstrate the identification of a molecular pathway directly linking insulin signalling with BA pool composition in mice, which translates to human pathophysiology. The functional consequences of this pathway are being investigated by multiple research groups.



	Name	Hydroxylations	Conjugates
CA	Cholic acid	3α, 7α, 12α	GCA, TCA
DCA	Deoxycholic acid	3α, 12α	GDCA, TDCA
CDCA	Chenodeoxycholic acid	3α, 7α	GCDCA, TCDCA
LCA	Lithocholic acid	3α	GLCA, TLCA
UDCA	Ursodeoxycholic acid	3α, 7β	GUDCA, TUDCA
αMCA*	α–Muricholic acid	3α, 6β, 7α	GαMCA, TαMCA
βMCA*	β–Muricholic acid	3α, 6β, 7β	GβMCA, TβMCA
ωMCA*	ω–Muricholic acid	3α, 6α, 7β	GωMCA, TωMCA

Fig. 1 |. Bile acid synthesis, modification and physicochemical properties.

a | Bile acid (BA) synthesis occurs only in the liver. In the classic pathway of BA synthesis, cholesterol is hydroxylated in the 7α position by the enzyme CYP7A1. Alternatively, cholesterol is first converted to an oxysterol prior to being 7α-hydroxylated by the enzymes CYP7B1 or CYP39A1. These oxysterols can arise in the liver, through the enzyme CYP27A1, or they can arise in other cells — such as macrophages via CYP27A1 or brain via CYP46A1 — then travel to the liver. After the initial step, which is considered rate-limiting, over a dozen enzymatic reactions proceed to generate the primary BA molecule chenodeoxycholic acid (CDCA). An intermediate in BA synthesis, 7α-hydroxy-4-cholesten-3-one, can undergo 12α-hydroxylation by the enzyme CYP8B1 and subsequently proceed through the additional steps. This process results in the generation of the second primary BA found in humans, cholic acid (CA). BAs are conjugated to an amino acid such as glycine (G) and secreted into the bile. BAs enter the duodenum directly or are stored in the gallbladder until postprandial gallbladder contraction. Most BAs are reabsorbed from the terminal ileum by the active transporter apical sodium-dependent bile acid transporter (ASBT). A minor fraction travel into the colon where they can be deconjugated and dehydroxylated by gut microorganisms, producing BAs that can be passively absorbed. From the portal vein, BAs are efficiently taken up into hepatocytes and recycled. A small fraction enter the systemic circulation. **b** | The major BA species found in humans and mice. **c** | Schematic demonstrating the amphipathic nature of BAs. *αMCA, βMCA and ωMCA are abundant in mice and rats but not humans.

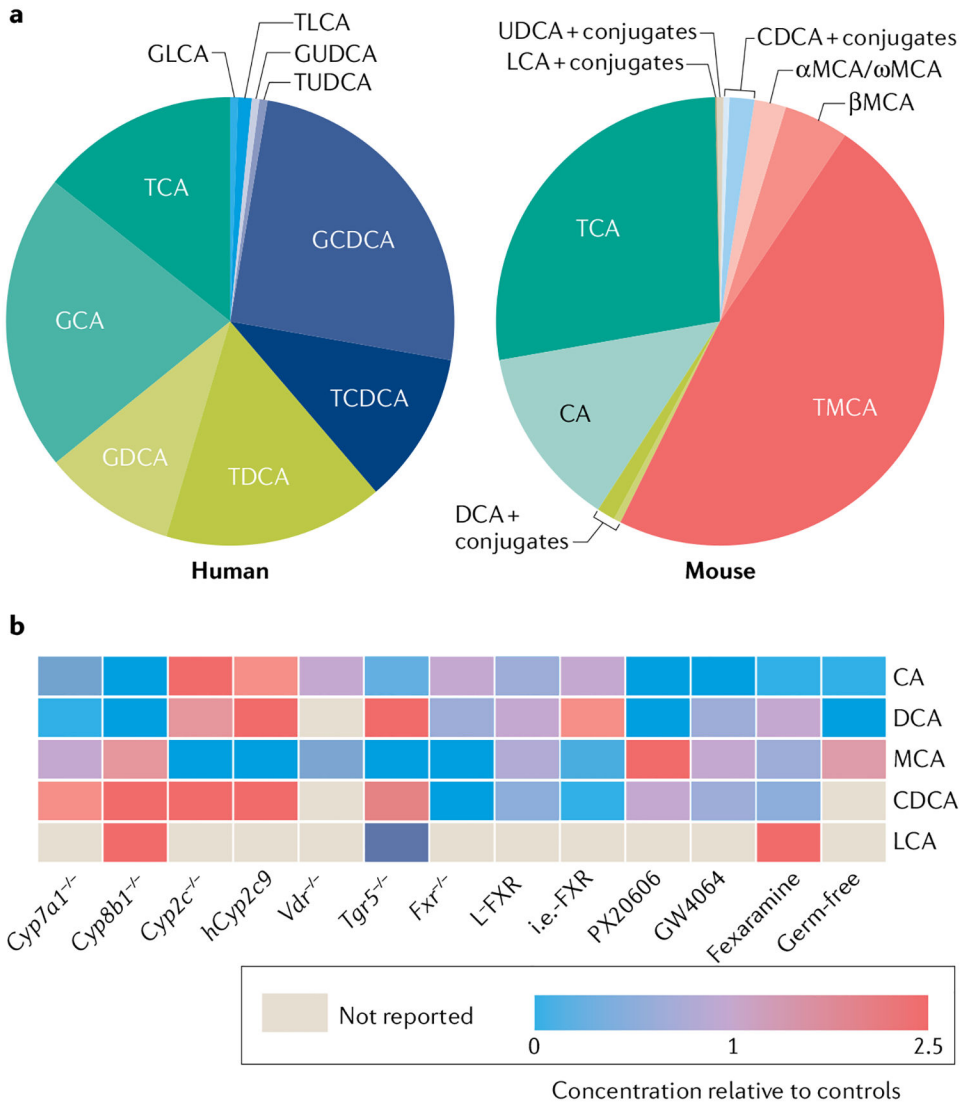


Fig. 2 |. Bile acid composition.

a | Average bile acid (BA) composition in human biliary bile (left) and in enterohepatic tissues (including bile) of wild-type mice (right). Human biliary bile data are averages from REFs[142–144]. Mouse BA pool data are averages from 58 wild-type mice across multiple studies including own published and unpublished studies. TMCA represents the sum of taurine-conjugated α-, β- and ω-muricholic acids (MCA). **b** | Effects of genetic knockouts[38,182,187–190] and pharmacological treatments[43,45,191,192] on mouse BA composition. Data for each BA species are the sum of conjugated and unconjugated BAs, and were calculated as (the percentage in the experimental pool/the percentage in the control pool). PX20606 and GW4064 are farnesoid X receptor (FXR) agonists. Fexaramine is a gut-restricted FXR agonist. In germ-free mice, no unconjugated BAs are detected. CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; GCA, glycocholic acid; GCDCA, glycochenodeoxycholic acid; GDCA, glycodeoxycholic acid; GLCA, glycolithocholic acid; GUDCA, glycoursodeoxycholic acid; i.e.-FXR, intestine epithelium-specific FXR knockout; L-FXR, liver-specific FXR knockout; LCA, lithocholic acid; TCA,

taurocholic acid; TCDCA, taurochenodeoxycholic acid; TDCA, taurodeoxycholic acid; TLCA, taurolithocholic acid; TUDCA, tauroursodeoxycholic acid; UDCA, ursodeoxycholic acid.

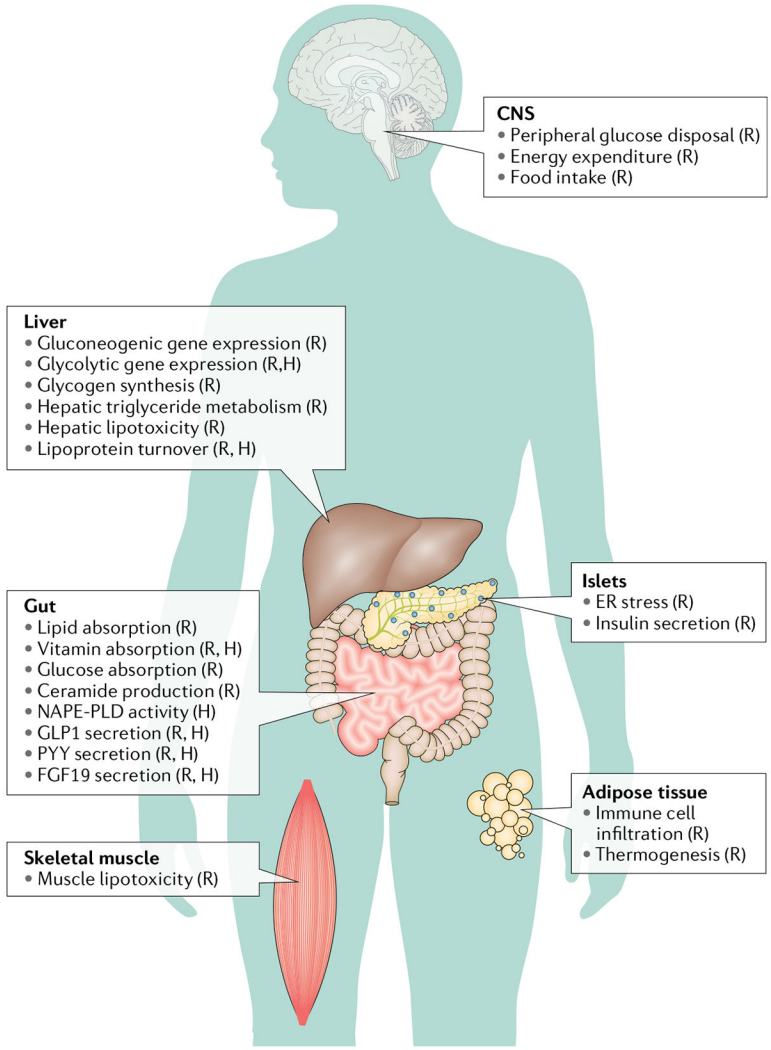


Fig. 3 |. Effects of bile acids on metabolic processes throughout the body.

The primary sites of bile acid (BA) function are the liver and intestine, which are enriched in BAs and BA receptors. Through their ability to facilitate secretion of hormones such as glucagon-like peptide 1 (GLP1), fibroblast growth factor 19 (FGF19) and others, BAs can indirectly affect other tissues, including the brain. Furthermore, low levels of BAs are found in the systemic circulation, potentially enabling direct effects of BAs in tissues throughout the body. (R) indicates that supporting data were mostly from rodents; (H) indicates that supporting data were from humans, human cells or purified human proteins. Data were originally presented in the following effects in the central nervous system (CNS): peripheral glucose disposal[59] (R), energy expenditure[58] (R), and food intake[193] (R); effects in islets: endoplasmic reticulum (ER) stress[33,173] (R), and insulin secretion[194] (R); effects in the liver: gluconeogenic gene expression[48,56] (R), glycolytic gene expression[52,216] (R, H), glycogen synthesis[57] (R), hepatic triglyceride metabolism[195] (R), hepatic lipotoxicity[48] (R), and lipoprotein turnover[152,196] (R, H); effects in adipose tissue: immune cell infiltration[91] (R), and thermogenesis[58]; effects in the gut: lipid absorption[13,183,184] (R), vitamin absorption[197] (R, H), glucose absorption[49] (R), ceramide production[50,198] (R), *N*-acyl

phosphatidylethanolamine phospholipase D (NAPE-PLD) activity[36,37] (purified human protein), GLP1 secretion[86–90,199] (R, H), peptide YY (PYY) secretion[90,199] (R, H), and FGF19 secretion[199] (R, H); and effects in skeletal muscle: lipotoxicity[48] (R).

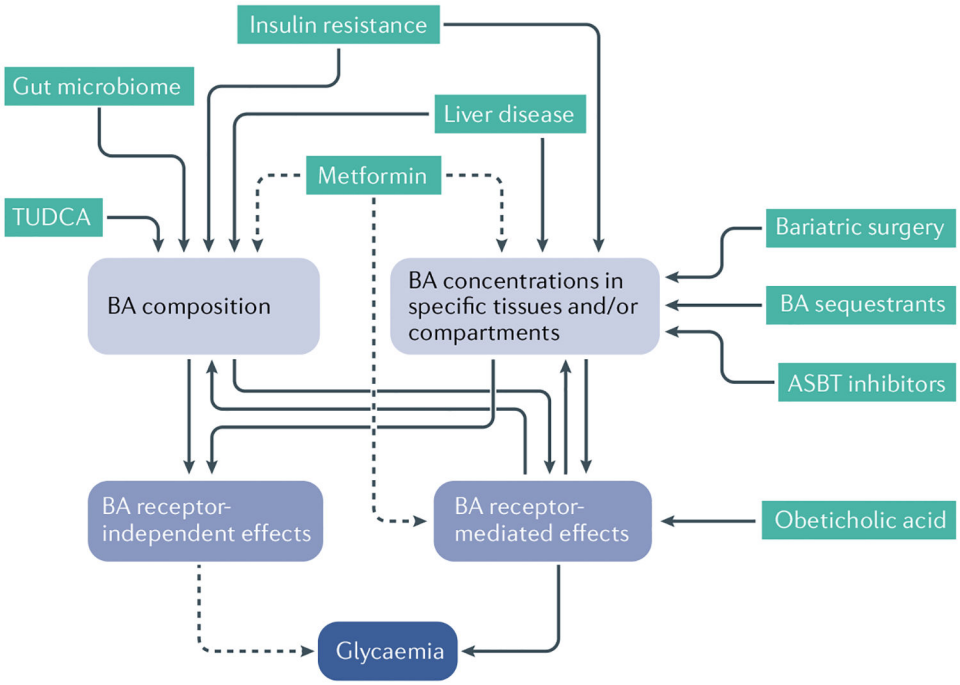


Fig. 4 |. Physiological and pathological conditions and therapies that influence bile acids.
An individual's total levels of bile acids (BAs), levels in selected tissues such as the gut or plasma, and the composition of those bile acid species can each influence bile acid functions. These include functions mediated by receptors such as FXR and TGR5, as well as receptor-independent effects, such as nutrient absorption. Green boxes represent conditions, medications and interventions that can affect BAs. Solid lines represent known pathways that affect and/or are affected by BAs. Dotted lines represent potential pathways. ASBT, apical sodium-dependent bile acid transporter; TUDCA, tauroursodeoxycholic acid.

Table 1 |

Concentrations of bile acids found in human tissues and compartments

Tissue	Concentration	Refs[a]
Systemic plasma and/or serum	0.2–22.0 μM	104,200,201
Portal venous plasma and/or serum	9–43 μM	200,202,203
Gallbladder bile	31–234 mM	143,144
Common bile duct	42–204 mM	142,204
Duodenum contents — fasting	0.3–9.6 mM	205,206
Duodenum contents — postprandial	8.3–11.9 mM	206
Jejunum contents — fasting	0.8–5.5 mM	205
Jejunum contents — postprandial	5–8 mM	207
Upper ileum contents — postprandial	10 mM	207
Lower ileum contents — postprandial	2 mM	207
Caecum contents	0.2–1 mM	208
Faeces	~4.5 μmol/g	209
Liver (liver biopsies contain bile canaliculi and ducts in addition to hepatocytes)	~60 nmol/g	130,210
Subcutaneous white adipose tissue	~0.2 nmol/g	201

[a]Different studies quantified BA levels using different extraction methods, different blood specimen processing methods (plasma versus serum), and different chromatography and mass spectrometry techniques. The individual references should be consulted for details.

Table 2 |

Individual effects of bile acids on bile acid receptors

Bile acid	FXR EC_{50}	FXR IC_{50}	TGR5 EC_{50}	VDR EC_{50}	PXR EC_{50}
Cholic acid	100–200 μM[197]	NA	7.72 μM[85], >10 μM[84], 13.6 μM[213]	No effect[211]	No effect[211]
Deoxycholic acid	50 μM[42], 50–75 μM[212]	NA	1.01–1.25 μM[85,213]	No effect[211]	50.2 μM[211]
Chenodeoxycholic acid	1–2 μM[212], 4.5 μM[40], 5.2 μM[185], 7 μM[75], 10 μM[41,212], (T, G) 10 μM[40], 10–30 μM[214], 20 μM[41,212], 25–50 μM[212], 50 μM[42]	NA	4–4.43 μM[84,85], (T) 1.92 μM[213], (G) 3.88 μM[199]	No effect[211]	(T) 104 μM[211]
Lithocholic acid	50 μM[42]	NA	35 nM[84], (T) 0.33 μM[85], 0.53 μM[85], 3 μM[84]	8 μM[41], 12.1 μM[215], 21.6 μM[211]	10.2 μM[211]
3-Keto-lithocholic acid	NA	NA	NA	3 μM[75], 6.8 μM[215]	8.3 μM[211]
Ursodeoxycholic acid	No effect[40]	NA	36.4 μM[213], No effect[85]	No effect[75]	NA
α-Muricholic acid	NA	(T) 28 μM[191]	NA	101.7 μM[211]	56 μM[211]
β-Murichoiic acid	NA	(T) 40 μM[202]	NA	No effect[211]	No effect[211]
Hyodeoxycholic acid	NA	NA	31.6 μM[213]	NA	NA

Note that different studies used different systems (cell lysates and different cell lines) and methods (such as, competitive binding assays, cAMP levels, cAMP-responsive luciferase reporter) to determine EC50 and IC50 values. The individual references should be consulted for details. EC_{50}, the effective concentration for a half maximal response; FXR, farnesoid X receptor; G, values specifically for glycine conjugates; IC_{50}, the concentration that reduces the response by half; NA, not applicable; PXR, pregnane X receptor; T, values specifically for taurine conjugates; TGR5, Takeda G protein-coupled receptor 5; VDR, vitamin D receptor.