



TOPICAL REVIEW

Bile acids, bioactive signalling molecules in interoceptive gut-to-brain communication

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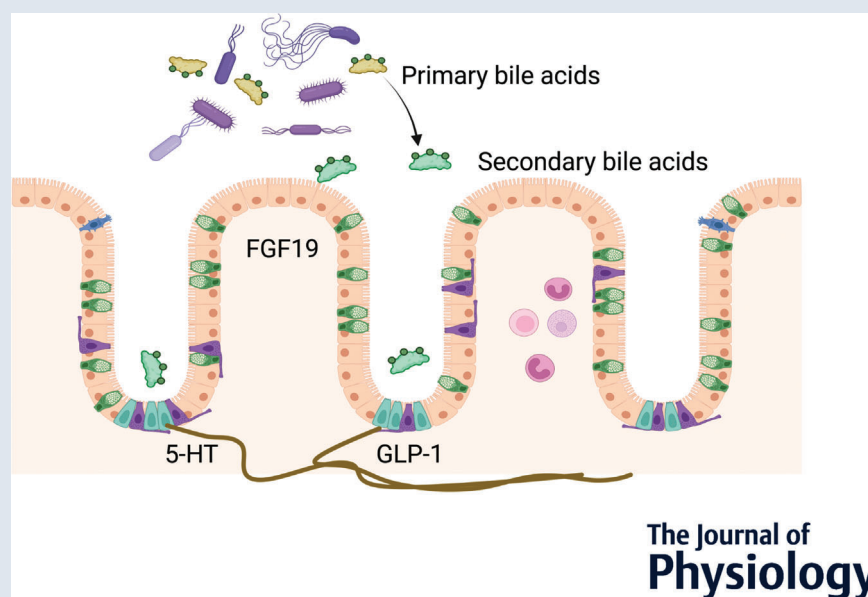
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Abstract Aside from facilitating solubilisation and absorption of dietary lipids and lipid-soluble vitamins, amphipathic bile acids (BAs) also act as bioactive signalling molecules. A plethora of conjugated or unconjugated primary and bacterially modified secondary BA moieties have been identified, with significant divergence between species. These molecules are excreted into

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the external environment of the intestinal lumen, yet nuclear and membrane receptors that are sensitive to BAs are expressed internally in the liver, intestinal and neural tissues, amongst others. The diversity of BAs and receptors underpins the multitude of distinct bioactive functions attributed to BAs, but also hampers elucidation of the physiological mechanisms underpinning these actions. In this Topical Review, we have considered the potential of BAs as cross-barrier signalling molecules that contribute to interoceptive pathways informing the central nervous system of environmental changes in the gut lumen. Activation of BAs on FGF₁₉-secreting enterocytes, enteroendocrine cells coupled to sensory nerves or intestinal immune cells would facilitate indirect signalling, whereas direct activation of BA receptors in the brain is likely to occur primarily under pathophysiological conditions when concentrations of BAs are elevated.

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Abstract figure legend Illustration of the microbial modification of hepatic primary bile acids into secondary bile acids. In addition to facilitating lipid digestion and absorption, bile acids act as bioactive signalling molecules by binding to bile acid receptors expressed on enterocytes, neural afferent-coupled enteroendocrine cells and immune cells.

Context

The continuous flow of information between the brain and the gut is significant in the context of maintaining physiological homeostasis (Mayer, 2011). Neural, immune, endocrine and metabolic pathways have all been implicated in this communication axis. Moreover, accumulating evidence, providing microbes with a role in modulating brain function and host behaviour (Stilling et al., 2015), has resulted in renaming of this bidirectional circuit as the microbiota–gut–brain axis (Bienenstock et al., 2015; Chakrabarti et al., 2022). Microbes interact with the host immune system and are also capable of stimulating sensory enteroendocrine cells (El Aidy et al., 2015; O'Malley, 2016). However, they also have an innate capacity to produce neuromodulatory factors, including central neurotransmitters and short-chain fatty acids (Fung et al., 2021; Lyte, 2014). Increasing attention is also being focused on the dynamic, symbiotic relationship that exists between bacteria with bile salt hydrolase (BSH) activity and luminal bile acids (BAs).

Most physiologists have familiarity with the digestive function of BAs, where their amphipathic structure enables solubilisation and absorption of dietary lipids and fat-soluble vitamins in the proximal intestine. However, given that numerous cell types, both in the gut and in other peripheral and central organs, express BA receptors (Deutschmann et al., 2018; Gadaleta, Oldenburg et al., 2011; Jonas et al., 2019; Ward et al., 2013), BAs are also classified as bioactive signalling molecules. The primary human BAs, cholic acid (CA) and chenodeoxycholic acid (CDCA), are synthesised and conjugated by liver hepatocytes. Conjugation makes BAs more soluble in the aqueous environment of the intestinal lumen and minimises potentially damaging interactions between BAs and

apical facing plasma membranes. The majority of BAs are transported from the distal ileum back to the liver via the portal vein as part of the entero-hepatic cycle. However, a small proportion escape reuptake and pass into the colon, the gut region where BSH-comprising bacteria are most abundant. Interactions between BSH-bacteria and primary BAs result in deconjugation reactions, which in turn facilitate further microbially mediated transformations. BSH activity is a ubiquitous trait in gut-residing bacteria, which may have evolved through host-driven selection (Jones et al., 2008). Dynamic interactions between microbes and BAs result in a great diversity of microbially modified secondary BA species (Guzior & Quinn, 2021), including deoxycholic acid (DCA) and lithocholic acid (LCA), in a variety of conjugated and unconjugated forms (Fig. 1). There are many receptors which bind BAs, with variable binding affinities and response potencies, resulting in a multitude of distinct bioactive functions. However, we will focus on the two BA receptors that exclusively bind BAs, nuclear farnesoid X receptors (FXR) and membrane-expressed G protein-coupled BA receptor 1 (GPBAR-1), also named Takeda G-protein-coupled receptor 5 (TGR5). In the context of this rapidly evolving research field, we have examined BAs as potential signalling molecules participating in interoceptive signalling from the intestines to the central nervous system (CNS).

Bile acid synthesis and secretion

BAs are a class of metabolites that interact with microbiota and have significant importance both in gut and whole-body homeostasis (Chavez-Talavera et al., 2017).

Location-specific changes in concentrations and diversity of BAs are influenced by diet, host metabolites and microbial interactions (Chiang & Ferrell, 2020). Derived from cholesterol, BAs are the major component of hepatic bile and act as lipid emulsifiers in the small intestine. Two inter-regulated pathways, the classical pathway in the endoplasmic reticulum, regulated by cytochrome CYP7A1, and the alternative pathway in the mitochondria, regulated through cytochromes CYP27A1 and CYP8B1, produce CA and CDCA, together and separately, respectively. Regulation of all three enzymes is mediated through microbial actions on the liver (Sayin et al., 2013) and the flux through each pathway can be altered by cholesterol cell localisation and overload (Ren et al., 2004) and by endoplasmic reticulum stress (Henkel et al., 2017). Therefore, all cells and tissues carrying mitochondria have the potential to produce CDCA.

BAs classically function at a critical micelle concentration to spread or emulsify fats for digestion and for cellular uptake from the gut lumen. The critical micelle concentration is different for individual BA moieties. This is important when considering microbial modifications of BAs and in the context of the sometimes-convergent nature of BA representation called signatures, associated with different disease states. To reduce their pK_a and optimise the critical micelle concentration, BAs are conjugated to an amino acid, usually taurine or glycine, which represent approximately 25% and 75%, respectively, of conjugates in humans. Variations in the ratios of glyco- and tauro-conjugated BAs are influenced by host enzymes and also by diet. Glycine conjugation is favoured in adult humans, pigs and cows, where vegan or herbivorous diets are more prevalent (Vessey, 1978), whereas in animals with an omnivorous or carnivorous diet, BAs are primarily

conjugated to taurine. In new-borns, taurine-conjugated BAs predominate and indeed, liver taurine levels are higher in infants. Interestingly, in the first week of life CA is the main BA with representation of CA:CDCA as being 2.5:1; this normalises in the first month of life to 1.2:1 (Murphy & Signer, 1974). Conjugated BAs in areas of low pH are toxic to some bacteria and may influence gut residency and colonisation resistance (Ducarmon et al., 2019). Other modifications, such as glucuronidation or sulphonation, target BAs for excretion (Takikawa et al., 1985), although all of these BA modifications can be reversed by gut bacteria.

Functionally, BAs act as signalling molecules by binding to and activating BA receptors, of which there are many. However, only two bind BAs exclusively. Activation of nuclear FXR is key to regulating *de novo* BA synthesis (Laffitte et al., 2000). Indeed, mice lacking FXR exhibit BA dyshomeostasis (Degirolamo et al., 2015), in addition to defects in lipid metabolism (Hanniman et al., 2005), changes in centrally regulated behaviours (Huang et al., 2015) and immune response (Gadaleta, van Erpecum et al., 2011). Membrane-expressed GPBAR-1 or TGR5 is a G-protein-coupled BA receptor, which induces cyclic adenosine monophosphate (cAMP) synthesis leading to activation of the protein kinase-A pathway and gene transcription (Kawamata et al., 2003). LCA is the most potent natural agonist of TGR5 (Kawamata et al., 2003), and has been shown to influence glucose metabolism, neuronal function, immune system control and liver regeneration (Guo et al., 2016).

There is, however, significant variability in receptor binding affinity and response potency, depending on BA species and conjugation state, resulting in a plethora of biological outcomes. It is important to note that

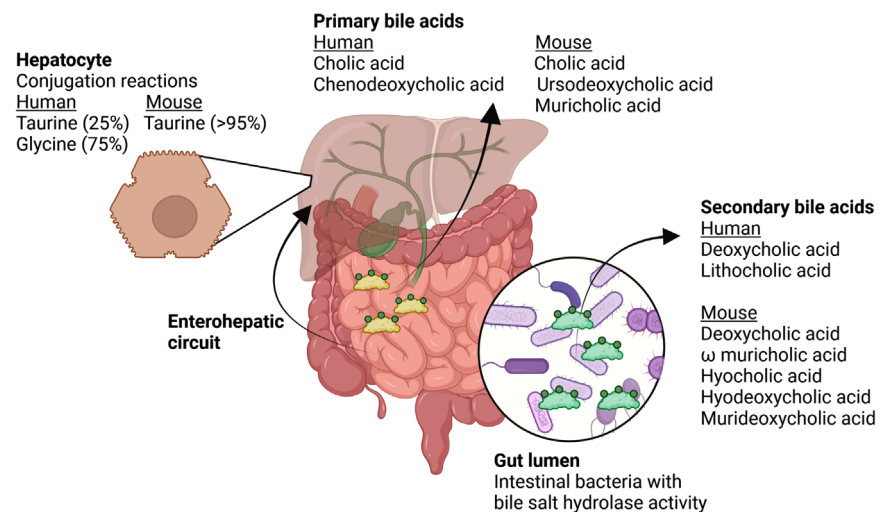


Figure 1. Species divergence in bile acid profiles

The figure illustrates the critical role that luminal bacteria play in generating a diverse array of bile acids. It also highlights species differences between mice and humans in the range and conjugation status of bile acids.

significant species diversity exists between rodents and humans. In mice, the primary BAs are CA and α - and β -muricholic acid (MCA), which is derived from CDCA through the actions of 6β -hydroxylase. Ursodeoxycholic acid (UDCA), a primary BA in mice but a 'tertiary' bile acid in humans, is a weak TGR5 agonist (Carino et al., 2019) and neutral toward FXR. 6β -Hydroxylation alters the physicochemical properties of BAs, such that these molecules are more hydrophilic but less potent detergents. The signalling properties of murine BAs is also significantly altered as CDCA, the most potent endogenous FXR agonist, is converted into MCA, which is actually an FXR antagonist (Guo & Chiang, 2020). Additionally, murine BAs are almost exclusively conjugated to taurine (Dawson & Karpen, 2015) and differences in rodent microbial profiles results in different secondary bile acids (Fig. 1). These factors make it difficult to translate observations from rodent studies to human conditions. Indeed, FXR agonists, which exhibited promise in experimental models of chronic liver disease (Ali et al., 2015), have not been as successful in humans. For example, the efficacy of FXR agonists for the treatment of non-alcoholic steatohepatitis was limited by dose-related side effects (Fiorucci et al., 2020).

Interactions between bile acids and intestinal microbes

The human body is host to its own unique, co-evolved microbial ecosystems where microbes (bacteria, viruses and fungi) reside. Bacteria have evolved to occupy specific spatial and temporal intestinal niches. They can form complex, sometimes symbiotic interactions with the host, as well as syntrophic interactions with other microbes. These interactions result in microbially produced factors and metabolites that may act as signalling molecules. The functional diversity of the intestinal tract confers on it the capacity to both impact and indicate health and disease status (Long et al., 2017). Modern meta-omics approaches have made characterisation and connection possible. Meta-genomics identify microbes and their genetic potential, meta-transcriptomics examine potential functionalities, meta-proteomics identify expressed functionality and meta-metabolomics assess the metabolites and actual functional outcomes. The major phyla (>90%) represented in the mature gut are Firmicutes and Bacteroidetes (Hugon et al., 2015). Diet, immunity and genetics add further to the complexity of microbial intestinal colonisation, enrichment and its associated metabolism (Scepanovic et al., 2019). Indeed, debate continues regarding the features of a healthy microbiota and its associated healthy metabolic capacity (Moya & Ferrer, 2016).

In the absence of a gut microbial community, BA moieties would have remained a conservative set of molecules. Bacterial enzymatic modifications in the gut lumen are responsible for the huge diversity of BAs detected regionally in the liver, the gut, the systemic circulation (Staley et al., 2017) and even the brain (Zheng et al., 2016), breast milk (Forsyth et al., 1983) and ovarian follicles (Yang et al., 2021). Often, secondary bile acids are more potent agonists for BA receptors (Ridlon et al., 2016). The gatekeepers, microbial BSHs, are a ubiquitous feature of almost all phyla represented in the gut environment (Jones et al., 2008). BSHs belong to the N-terminal nucleophile (Ntn) hydrolase superfamily of proteins. Discovered in 1995, these enzymes hydrolyse the amide bond conjugated to the BA steroid nucleus and differ in their substrate specificity (Brannigan et al., 1995). Individual species of bacteria can carry none, one or indeed multiple copies of BSHs (Fang et al., 2009; Prete et al., 2020), which may or not be active. These enzymes selectively remove the amine from liver-conjugated BAs, rendering them susceptible to further modification by microbes (Joyce et al., 2014; Song et al., 2019).

BSH activity may confer a protective advantage for bacterial species survival and colonisation, so that BSH activity is among the selection criteria for probiotics (Jones et al., 2008; Vizoso Pinto et al., 2006). Additionally, in liberating amino acids, glycine and taurine, bacteria may be able to use these amino acids as an energy source. Therefore, another role for conjugated BAs could be to carry these amino acids to the intestines for further use, or alternatively, to act as a sink for nitrogen elimination in the faeces. BAs that escape ileal uptake and dihydroxylation can undergo microbial re-amidation, oxidation esterification, deglucuronidation and desulphatation (Quinn et al., 2020; Ridlon & Hylemon, 2012; Ridlon et al., 2006). BAs that have undergone oxidation, epimerization and dehydroxylation are usually recycled to the liver, repaired and re-secreted into bile, whereas the majority of BAs excreted in the faeces are products of 7α -dehydroxylation (Hirano et al., 1981).

Direct bile acid signalling in the central nervous system

Only a small proportion of BAs escape the enterohepatic circuit to gain entry to the systemic circulation allowing them to function as steroid hormones. However, with the exception of UDCA and tauro-UDCA, which can cross the blood-brain barrier at physiological concentrations, most BAs are restricted to the peripheral circulation (Parry et al., 2010). Nonetheless, BA receptors including TGR5 (Keitel et al., 2010) and FXR (Huang et al., 2016) have been detected in neurons, astrocytes and microglia in the brain. Indeed, endogenous neurosteroids

also bind to TGR5, resulting in increases intracellular cAMP and calcium (Keitel et al., 2010). Neurosteroids have been implicated in the pathological consequences of hepatic encephalopathy in the CNS. In a mouse model of hepatic encephalopathy, activation of TGR5 is protective against neurological decline evoked, by suppressing neuroinflammation (McMillin, Frampton, Tobin et al., 2015). The brain also represents a potential site of BA synthesis. Indeed, twenty BAs and oxysterols were detected in rat brain regions (Zheng et al., 2016). Altered CYP8B1 and CYP7A1 expression were also detected in human brain tissue (Cali et al., 1991; Ogundare et al., 2010). Additionally, when serum BAs are at supra-physiological concentrations, as in the case in cholestasis, a leaky blood–brain barrier facilitates passive movement of BA into the CNS. In an animal model of cholestasis, specific BAs were taken up into hypothalamic neurons, which express BA transporters (McMillin, Frampton, Quinn et al., 2015), resulting in suppression of corticotropin-releasing factor (CRF) synthesis and secretion (Quinn et al., 2014). Others have reported that BAs have an indirect inhibitory effect on the hypothalamic–pituitary–adrenal (HPA) stress axis, either through their actions on glucocorticoid receptors (McMillin, Frampton, Quinn et al., 2015) or by suppression of hepatic glucocorticoid clearance (McNeilly et al., 2010).

CRF is secreted as part of an adaptive response to a perceived environmental threat and thereby activates HPA axis activity. Chronic activation of the HPA axis is associated with altered bowel morphology, function and visceral pain sensitivity (O'Malley et al., 2010; Parker et al., 2019) and is frequently co-morbid in individuals with the functional bowel disorder, irritable bowel syndrome (IBS) (Spiller, 2004). Stress and the subsequent activation of the HPA axis also impacts on the luminal environment of the gut, as noted by direct changes in luminal BA profiles (Silvennoinen et al., 2015) and indirect effects through modification of the microbiome (Madison & Kiecolt-Glaser, 2019). Although more research is needed to elucidate the precise consequences of BA-induced suppression of the HPA axis activity on gut luminal contents, an impaired stress response is associated with an inadequate host defence against pathogens and an imbalance in intestinal microbiota would, in turn, modify the BA pool. Thus, under certain pathophysiological conditions, BAs may influence central regulation of gut function (Ni Dhonnabhain et al., 2021).

Sensitivity of intestinal sensory nerves to bile acids

Intrinsic to a bidirectional axis are signalling conduits that inform the CNS about the luminal environment of the intestine. Direct and indirect neural, immune and

endocrine pathways facilitate this function (Mayer, 2011; Öhman et al., 2015). The versatility of BAs as signalling molecules is underpinned by widespread expression of both nuclear and membrane receptors throughout the organism, in addition to direct and indirect modes of signalling. BA profiles vary with diet, transit through the intestine and changes in the microbiome. Although not comparable to any human condition, germ-free mice, have proved extremely useful in investigating the capacity of luminal microbial factors to modify host physiology. Germ-free mice exhibit elevated levels of BAs and increased activation of membrane-expressed TGR5 receptors (Selwyn et al., 2015). In the absence of luminal microbes, intrinsic primary afferent neurons, proposed to be a neural starting point for the relay of information regarding the gut lumen to the brain, are less excitable (McVey Neufeld et al., 2015). TGR5 receptors have been detected on intrinsic primary afferent neurons (Alemi et al., 2013), indicating a possible neurally regulated signalling pathway. Moreover, activation of TGR5 receptors has been implicated in gut-to-brain satiety-related signalling via the vagus nerve (Wu et al., 2020). The vagus nerve appears to have a central role in mediating microbiome–CNS communication, as in mouse studies vagotomy prevented behavioural changes brought about by modifying the gut microbiome (Bercik et al., 2011; Bravo et al., 2011). Moreover, we and others have recorded changes in the excitability of rodent vagal afferents in the jejunum (Perez-Burgos et al., 2013, 2015) and colon (Buckley & O'Malley, 2018; Buckley et al., 2019, 2020) following mucosal exposure to specific bacterial products. As vagal afferent sensory endings are sensitive to oleanolic acid, a TGR5-specific agonist (Wu et al., 2020), they are appropriately equipped to facilitate neural transmission of information about BAs in the luminal environment, but further research is needed in this area.

Endocrine-mediated gut–brain signalling evoked by bile acids

Embedded within the intestinal epithelium are enteroendocrine cells, specialised chemosensors with luminal and basolateral sides. When activated, these polarised sensory cells release endocrine factors basolaterally (Raybould, 2010) and represent an indirect mode of interoceptive signalling. Expressing a multitude of receptors, luminal contents including nutrients, microbial products and BAs stimulate these sensory cells, resulting in release of endocrine or neuromodulatory molecules. BAs stimulate cholecystokinin-mediated gallbladder contraction, induction of lipase activity and pancreatic enzyme and bicarbonate release. In the colon, but not the small intestine, TGR5 is expressed on serotonin-secreting enterochromaffin cells

(Lund et al., 2018), which release serotonin when stimulated by bile salts. Interestingly, neoplastic enterochromaffin cells exhibit enhanced sensitivity to bile salt ligands (Kidd et al., 2008). Although serotonin cannot cross the blood–brain barrier, enterochromaffin cells are coupled to sensory nerves (Bellono et al., 2017), revealing a clear neural pathway to facilitate signalling between the gut lumen and the CNS.

Glucagon-like peptide-1 (GLP-1) and peptide YY (PYY)-secreting L-cells are another subset of enteric biosensors. Electrically excitable L-cells express an abundance of receptors including receptors for microbially produced factors such as short-chain fatty acids (Tolhurst et al., 2012), GABA (Gameiro et al., 2005), serotonin (Lund et al., 2018), as well as FXR and TGR5 both in rodents (Christiansen et al., 2019; Katsuma et al., 2005) and in humans (Calderon et al., 2020; Trabelsi et al., 2015). In isolated human enterocytes, almost three-quarters of GLP-1-expressing enteroendocrine cells were found to express TGR5, whereas only 16% of GLP-1 negative cells expressed the BA receptor, indicating that GLP-1-secreting L-cells are the predominant cell type activated by TGR5-stimulating BAs (Calderon et al., 2020). Stimulation of L-cells by potent TGR5 agonists, particularly LCA, increased intracellular cAMP and calcium resulting in secretion of GLP-1 (Parker et al., 2012). Moreover, elevated circulating concentrations of GLP-1 following inhibition of ileal BA transporters was explained by elevated luminal levels of BAs interacting with colonic L-cells (Rudling et al., 2015). It is noteworthy that TGR5 is expressed on the basolateral membrane of L-cells (Brighton et al., 2015; Calderon et al., 2020; Christiansen et al., 2019), indicating that BAs must first traverse the epithelial barrier to stimulate GLP-1 release from L-cells. GLP-1 receptors are expressed in several regions of the central nervous system (Baggio & Drucker, 2014) and this hormone may be able to cross the blood–brain barrier by simple diffusion (Kastin et al., 2002). However, the enzyme dipeptidyl peptidase-4 rapidly degrades circulating GLP-1, and therefore high concentrations of this hormone are primarily detected in the intestinal lamina propria. An alternative signalling pathway would be through neural signals generated in vagal afferents, which express GLP-1 receptors (Nakagawa et al., 2004; Ronveaux et al., 2014). Similar to the coupling of enterochromaffin cells with peripheral afferents (Bellono et al., 2017), L-cells also form a neuroepithelial circuit, directly synapsing with sensory afferents (Bohorquez et al., 2015), which signal to the CNS (Buckley et al., 2020). In this way, L-cells could act as sensory transducers to facilitate indirect transmission of cross-barrier sensory signals from luminal BAs to the CNS.

In contrast to the stimulatory action of conjugated BAs on the TGR5–GLP-1 signalling pathway, primary

BAs, which have a higher affinity for nuclear FXR, cause the release of FGF₁₉, which decreases expression of GLP-1 (Calderon et al., 2020). Furthermore, crosstalk between these receptors contributes to the regulation of glucose homeostasis (Kim & Fang, 2018), and functional antagonism has also been reported between these two BA receptors in the context of autophagy relating to fed and fasting states (Carino et al., 2021). These studies exemplify the complexity of BA signalling resulting in diverse biological outcomes. Activation of FXR in the terminal ileum induces secretion of FGF₁₉, which is transported via the portal vein to the liver where it stimulates hepatic fibroblast growth factor receptor (FGR) 4. FGR4 regulates *de novo* synthesis and mobilisation of hepatic BAs (De Magalhaes Filho et al., 2017). However, FGF₁₉ may also cross the blood brain barrier (Hsuchou et al., 2013) and bind to FGRs in select brain regions including the hypothalamus, where it may modulate feeding behaviour (Mertens et al., 2017), but could also impact upon gut function through activation of the HPA axis. This indirect signalling cascade, involving enteroendocrine cells and neural afferents, elucidates a potential pathway by which intestinal BA receptors could modify central neuro-circuitry (Fig. 2).

Bile acids stimulate immune signalling molecules

BAs exhibit antimicrobial properties as evidenced in the small intestine, where high bile concentrations prevent small intestinal bacterial overgrowth (Dawson & Karpen, 2015). Mechanistically, this may be mediated through direct cytotoxicity (Staley et al., 2017), or by stimulating innate immune mechanisms (D'Aldebert et al., 2009). One such mechanism employed to protect the intestinal epithelium from cytotoxic BAs is the stimulation of BA diarrhoea by high colonic levels of BAs (Hegyí et al., 2018). Moreover, monocytes, macrophages, dendritic and natural killer cells all express TGR5 and FXR receptors (Cipriani et al., 2011; Maruyama et al., 2002; Vavassori et al., 2009). Generally, it appears that BA moieties and their conjugates are important for fine-tuning the immune response to the diversity of antigens to which the gut is exposed (Sun et al., 2021), with a bias in favour of gut tolerance (Fiorucci et al., 2018). Indeed, TGR5-induced activation of monocytes and macrophages inhibits phagocytic activity and secretion of pro-inflammatory cytokines (Haselow et al., 2013; Perino et al., 2014; Pols et al., 2011). Cytokine and chemokine release from monocytes and dendritic cells is also suppressed following FXR activation, and overall it is protective against the effects of intestinal inflammation (Gadaleta, van Erpecum et al., 2011). Changes in BA pools impact on intestinal immune function (Fiorucci et al., 2021), both directly through their variable affinity

for different BA receptors on host immune cells and indirectly by modifying luminal microbial profiles. Previously largely ignored, formation of BA minor species or intermediates (Doden & Ridlon, 2021), as a consequence of mature secondary BA formation (DCA from CA, LCA and UDCA from CDCA), is important, as many are now being assigned roles as mediators of both innate and adaptive immunity (Campbell et al., 2020; Meng et al., 2018; Song et al., 2019). Given the established interactions between luminal factors and immune cells residing in the gut, the circulation and the CNS (Fung, 2020), BAs could also employ immune-mediated gut-to-brain signalling pathways (Buckley et al., 2014; O'Malley, 2016) in interoceptive communication with the CNS (Fig. 2).

Bile acid-mediated signalling under pathophysiological conditions

Diversity and richness of the gut microbiome is an indicator of good gut health (Human Microbiome Project Consortium, 2012), and this in turn appears to maintain a healthy diversity of BAs across the spectrum. However, in disease states, where gut microbial dysbiosis occurs, the expected consequence is alterations to the size and the diversity of the BA pool (Contijoch et al., 2019; Joyce et al., 2014). Elevated activity of BSH has been associated with inflammation (Parasar et al., 2019) and BSHs are central to the drive towards infection (Mullish et al., 2019), which could, in turn, influence immune-mediated signalling to the CNS. A role for microbes and BA signatures in intestinal and microbial health is clearly defined in

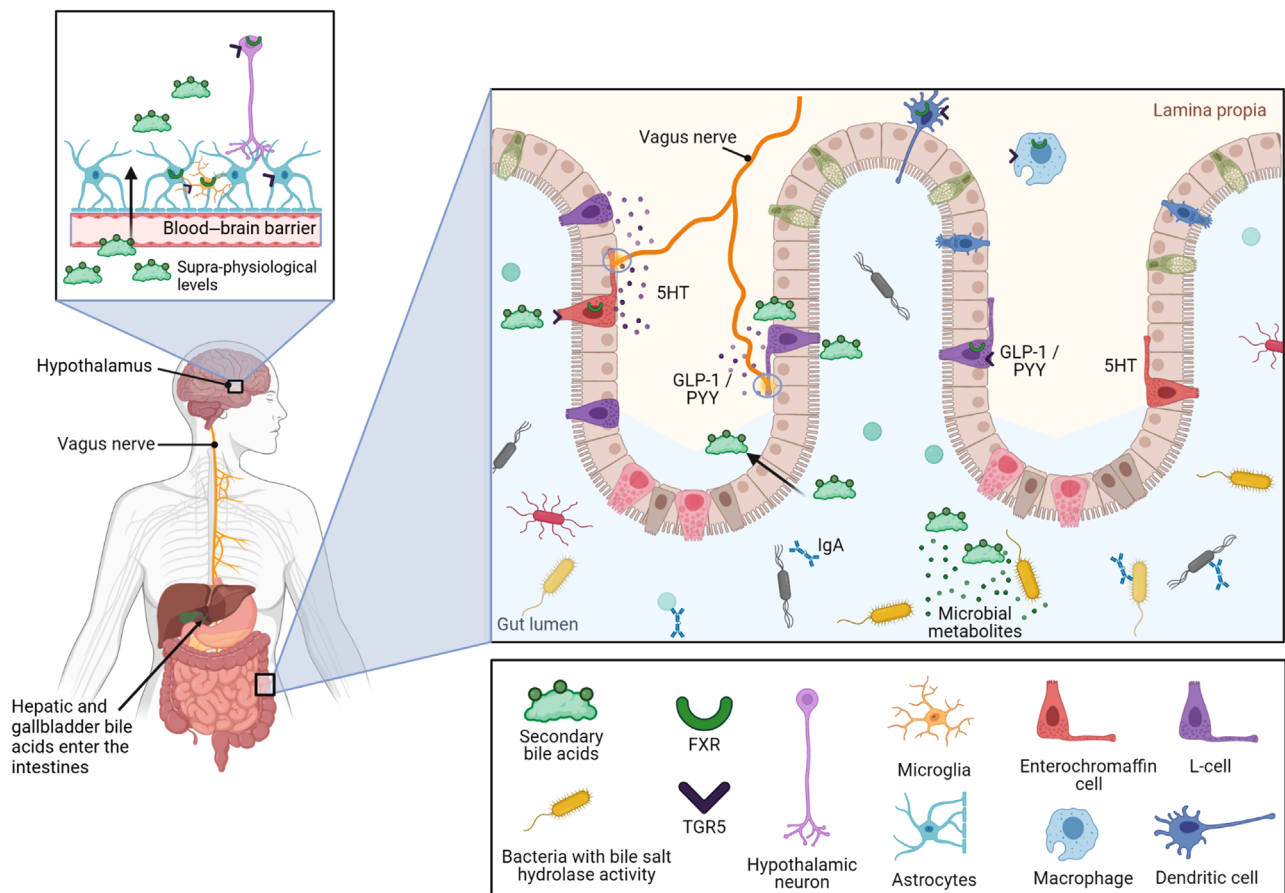


Figure 2. Bile acids as bioactive molecules in the gut–brain signalling axis

The illustration depicts interactions between colonic microbes with bile salt hydrolase activity and luminal bile acids (BAs). These BAs may subsequently bind to BA receptors, which are expressed on enteroendocrine, immune and neural cells. When circulating BA levels are elevated (under pathophysiological conditions), BAs may cross the blood–brain barrier and bind to TGR5 and FXR, which are expressed on neural cells, astrocytes and microglia. The figure is adapted from a 'Gut–brain axis' template, by BioRender.com (2021). Retrieved from <https://app.biorender.com/biorender-templates>

the incidence of recurrent *Clostridia difficile* infections, where microbial diversity is reduced through recurrent antibiotic use. This resulted in altered BA signatures characterised by loss of secondary BAs with a concomitant gain in primary BAs (Brown et al., 2018). Inflammatory bowel diseases (Crohn's disease and ulcerative colitis) are also linked to alterations in BA signatures. Faecal microbiota from individuals with inflammatory bowel disease is less diverse and more unstable (Pascal et al., 2017), and associations to inflamed and non-inflamed regions point to specific microbial drivers of inflammation and epigenetic regulation (Ryan et al., 2020). Although signatures differed, a common emerging theme in these patients was increased CA and a selective decrease in circulating secondary BAs (Duboc et al., 2013; Sinha et al., 2020; Weng et al., 2019).

It is generally accepted that manifestation of symptoms characteristic of the functional bowel disorder, IBS, is due to dysfunctional gut-brain communication (Enck et al., 2016). The gut microbiome is altered in IBS patients (Rajilic-Stojanovic et al., 2011). As deconjugated bile acids can drive microbial phylum-level shifts (Islam et al., 2011), changes in bacterial profiles mediated by bile acids may be a contributory factor in IBS. Indeed, chronic watery diarrhoea is a symptom of luminal accumulation of bile acids due to malabsorption (Conley et al., 1976; Coyne et al., 1976), and a subset (~25%) of individuals with IBS-D exhibit elevated faecal BAs resulting in accelerated colonic transit, which is linked with diarrhoea and visceral pain sensitivity (Slattery et al., 2015). Bile acids may also influence motility in this subtype (Peleman et al., 2017). Interestingly, treatment with colestipol, which binds BAs and prevents ileal reabsorption, improved IBS symptoms (Bajor et al., 2015). The therapeutic potential of BAs in functional bowel disorders is currently being explored (Rao et al., 2010).

Treatment with BAs may also have benefits in age-related cognitive decline. In mouse models of Alzheimer's disease, a neurodegenerative condition characterised by progressive cognitive impairment, dietary supplementation with tauro-UDCA positively altered amyloid plaque deposition and neuronal injury (Nunes et al., 2012) and in Parkinson's disease, defective mitochondrial function was in part restored on administration of UDCA (Mortiboys et al., 2013). Indeed, BA profiles change with age. In mouse studies, BA concentrations increased, particularly conjugated BAs and secondary BAs (Fu et al., 2012), whereas in humans the levels of BA-committed precursor 7 α -hydroxy-4-cholesten-3-one, was inversely correlated with ageing (Bertolotti et al., 2007). Interestingly, Sato et al. (2021) reported that the minor BA intermediates associated with immune cell differentiation were prevalent in centenarians. BA activities were related to enhanced pathogen resistance, and the authors speculated on their

roles in toxin clearance, better bone health and immune functions in maintaining health in ageing. Thus, host cell senescence in ageing goes hand-in-hand with microbial bacterial cell senescence leading to changes in BA profiles and BA-mediated signalling.

Concluding remarks

Gaining an understanding of the physiological mechanisms by which microbes, residing in the external environment of the intestinal lumen, influence interoceptive signalling from the gut to the brain has received substantial research interest in recent times. While it is generally accepted that a dynamic and interactive relationship exists between microbiota and BAs, the potential contribution of BAs as independent bioactive signalling molecules in gut-brain communication has been somewhat overlooked.

As discussed, BAs may signal to the CNS using both direct and indirect mechanisms (Fig. 2). Once in the systemic circulation BAs may operate as endocrine factors and cross the blood-brain barrier to directly bind to BA receptors expressed on neural cells in the brain. However, this appears to occur primarily under pathophysiological conditions when concentrations of BAs are elevated. Under physiological conditions, it is more likely that indirect pathways represent the predominant signalling conduits for BAs. This may be through activation of BA receptor-expressing enterocytes or enteroendocrine cells. Hormone-secreting biosensors release neuromodulatory factors such as serotonin and GLP-1 that have the capacity to stimulate vagal afferent fibres. An alternative signalling route is through activation of FXR-expressing enterocytes, which secrete FGF₁₉, a neuromodulatory factor that can cross the blood-brain barrier. Further research is needed to elucidate these possible signalling routes. Finally, we described the predominantly anti-inflammatory effects of BAs on the immune system and how changes to the BA pool could influence immune-mediated gut-to-brain signalling. Even when focused on a single class of signalling molecule such as BAs, the simplicity of the term 'gut-brain axis' belies the complexity of direct and indirect signalling pathways, which may be activated by a multitude of BA species which have variable affinities for several BAs' receptors. It has yet to be determined if the actions of nuclear or membrane receptor binding BAs have contrasting or complimentary effects in terms of interoceptive signalling. It is also not clear whether regional differences in BA profiles in the proximal and distal intestine relay distinct information to the CNS. Moreover, pathophysiological changes differentially modify these signalling pathways adding to the complexity. Much remains to be elucidated regarding the physiological mechanisms of these intriguing bioactive signalling molecules.

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Additional information

Competing interests

None.

Author contributions

S.J. and D.O.'M. prepared this review together. Both authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Supporting information

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