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

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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 un-conjugated primary and bacterially-modified secondary BA moieties have been identified, with significant divergence between species. These molecules are excreted into 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 FGF_{19}-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 are likely to occur primarily under pathophysiological conditions when concentrations of BAs are elevated.

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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 (Lyte, 2014; Fung *et al.*, 2021). Increasing attention is also being focussed 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 (Gadaleta *et al.*, 2011a; Ward *et al.*, 2013; Deutschmann *et al.*, 2018; Jonas *et al.*, 2019), 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, facilitates further

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microbially-mediated transformations. BSH activity is a ubiquitous trait in gut-residing bacteria that may have evolved through host-driven selection (Jones *et al.*, 2008). Dynamic interactions between microbes and BAs results 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 (figure 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.

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BAs classically function at a critical miceller concentration to spread or emulsify fats for digestion and for cellular uptake from the gut lumen. The critical miceller 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 pKa and optimise the critical miceller 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 herbivore diets are more prevalent (Vessey, 1978), whereas in animals with an omnivore or carnivore diet, BAs are primarily conjugated to taurine. In newborns, 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 *et al.*, 2011b). Membrane-expressed GPBAR-1 or TGR5 is a G-protein-coupled BA receptor,

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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 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 (figure 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 does-related side effects (Fiorucci *et al.*, 2020).

Interactions between bile acids and intestinal microbes

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The human body is host to its own unique, co-evolved microbial ecosystems where microbes (bacteria, virus 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 microbial-produced factors and metabolites that may act as signalling molecules. The functional diversity of the intestinal tract confers it with 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 asses 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*

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al., 2020), that 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 bacteria species survival and colonisation, so that BSH activity is among selection criteria for probiotics (Vizoso Pinto *et al.*, 2006; Jones *et al.*, 2008). 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 (Ridlon *et al.*, 2006; Ridlon & Hylemon, 2012; Quinn *et al.*, 2020). 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 central neurons and glial cells (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

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neurological decline evoked, by suppressing neuroinflammation (McMillin *et al.*, 2015b). 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 *et al.*, 2015a), 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 *et al.*, 2015a) 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

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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 have 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; Perez-Burgos *et al.*, 2015) and colon (Buckley & O'Malley, 2018; Buckley *et al.*, 2019; Buckley *et al.*, 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, however, further research is needed in this area.

Endocrine-mediated gut-brain signalling evoked by bile acids.

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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 all 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 (Katsuma et al., 2005; Christiansen et al., 2019) and humans (Trabelsi et al., 2015; Calderon et al., 2020). 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

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that TGR5 is expressed on the basolateral membrane of L-cells (Brighton et al., 2015; Christiansen et al., 2019; Calderon et al., 2020), 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, 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 FGF_{19}, which decreases expression of GLP-1 (Calderon et al., 2020). Furthermore, crosstalk between these receptors contribute 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 FGF_{19}, which is transported via the portal vein to the liver where is 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, FGF_{19} 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

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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 neurocircuitry (figure 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 (Hegyi et al., 2018). Moreover, monocytes, macrophages, dendritic and natural killer cells all express TGR5 and FXR receptors (Maruyama et al., 2002; Vavassori et al., 2009; Cipriani et al., 2011). 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 (Pols et al., 2011; Haselow et al., 2013; Perino et al., 2014). 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 *et al.*, 2011b). Changes in BA pools impacts 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 (Meng *et al.*, 2018; Song *et al.*, 2019; Campbell *et al.*, 2020). Given the established interactions between luminal factors and immune cells residing in the gut, the

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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 (figure 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, 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 BA pool (Joyce *et al.*, 2014; Contijoch *et al.*, 2019). 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 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; Weng *et al.*, 2019; Sinha *et al.*, 2020).

It is generally accepted that manifestation of symptoms characteristic of the functional bowel disorder, IBS, are due to dysfunction gut-brain communication (Enck *et al.*, 2016). The gut

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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 contributary 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 fecal BAs resulting in accelerated colonic transit, which is linked with diarrhea 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) and 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 TUDCA positively altered amyloid plaque deposition and neuronal injury (Nunes *et al.*, 2012) and in Parkinson's disease, defective mitochondrial function in 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 7alpha-hydroxy-4-cholesten-3-one, was inversely correlated with aging (Bertolotti *et al.*, 2007). Interestingly, Sato and colleagues reported that the minor BA intermediates associated with immune cell differentiation were prevalent in centenarians (Sato *et al.*, 2021). 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 aging. 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.

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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 (figure 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 $FGF_{19,}$ 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 focussed on a single 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

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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.

Additional Information Section

Competing Interests

No competing interests declared.

Author Contributions

SJ and DO'M prepared this review together. Both authors approved the final version of this manuscript. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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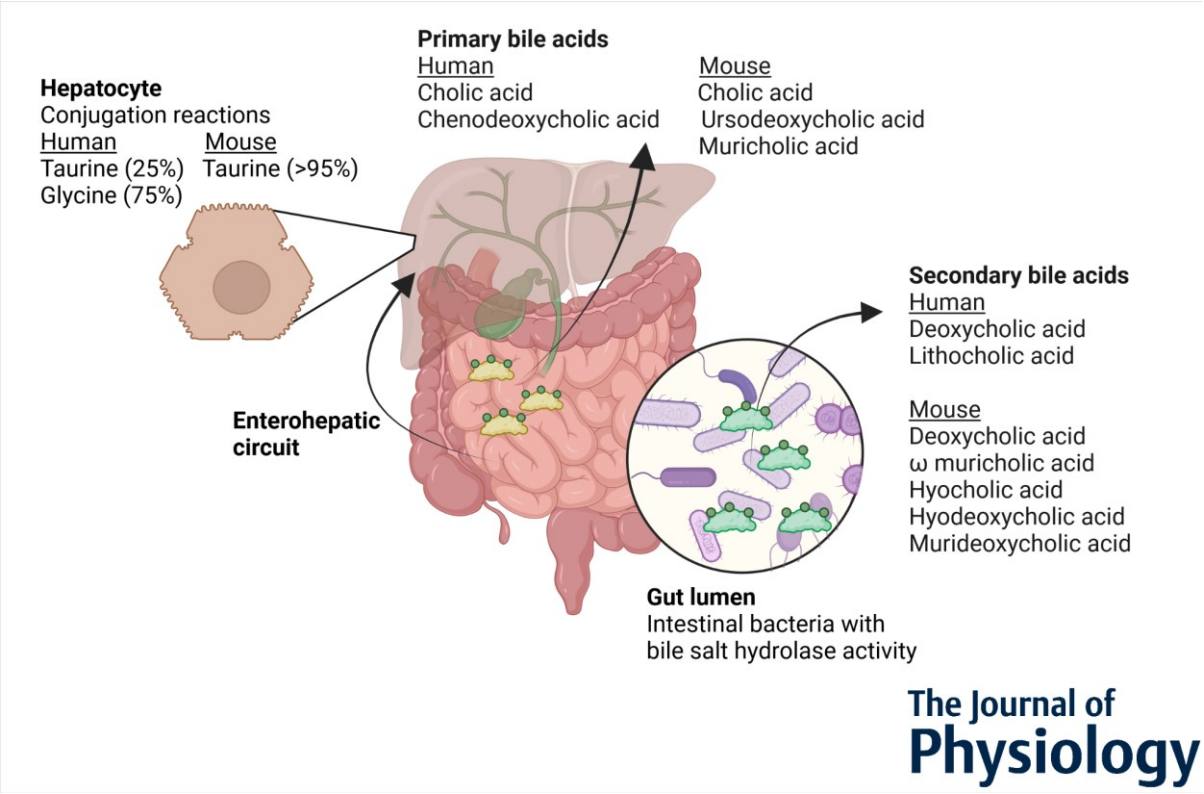
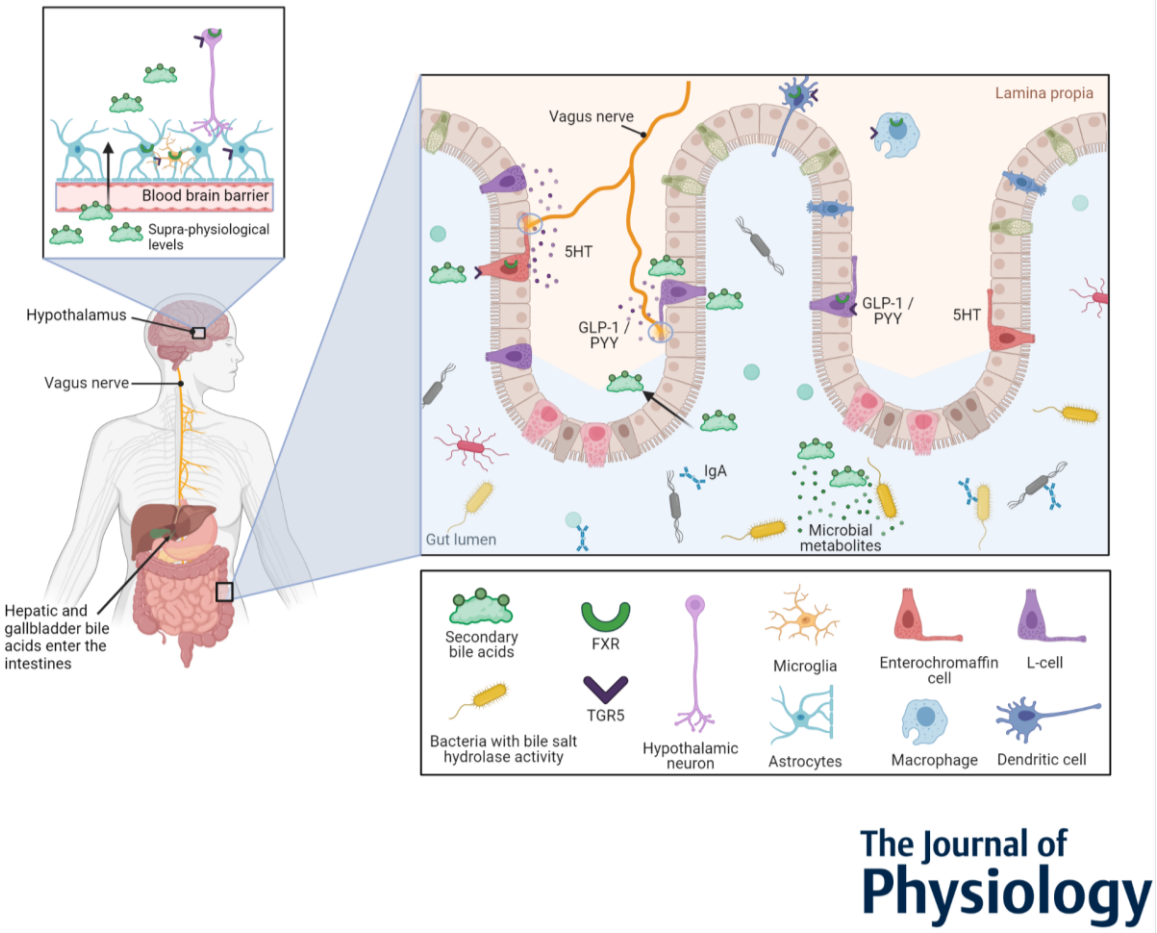


Figure 1: Species divergence in bile acid profiles.

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

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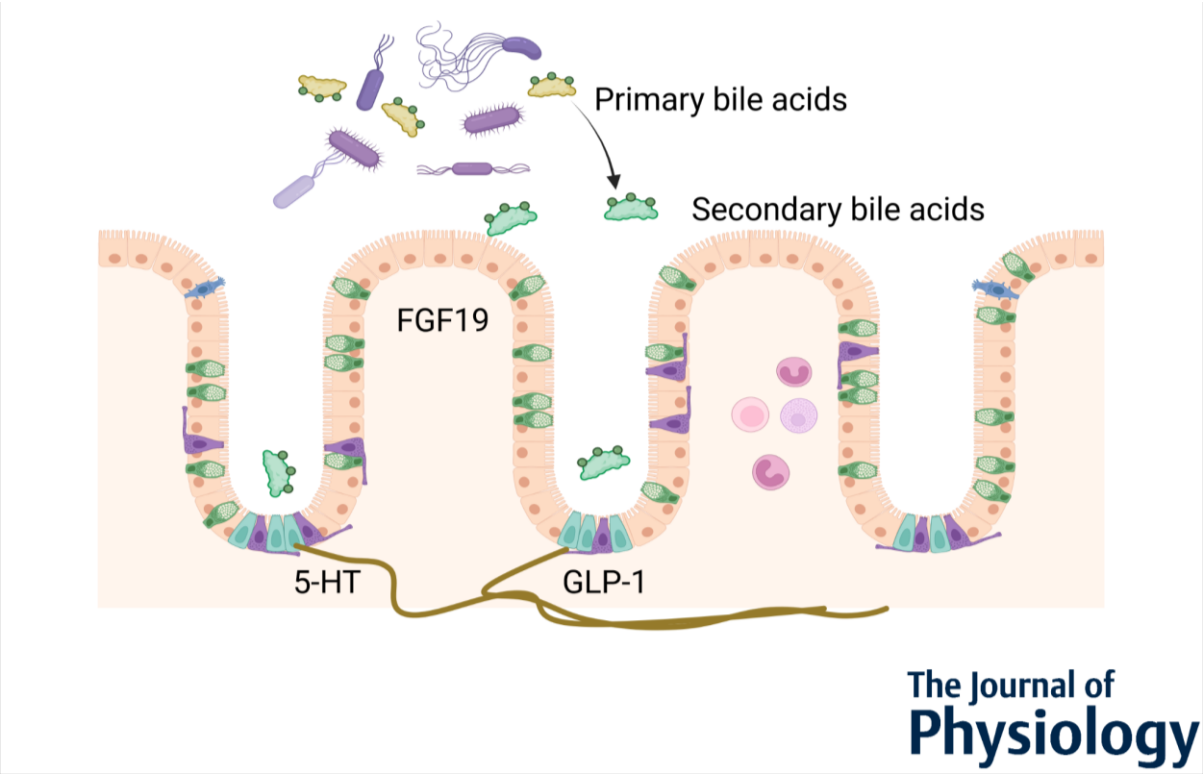
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Figure 2: Bile acids as bioactive molecules in the gut-brain signalling axis.

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

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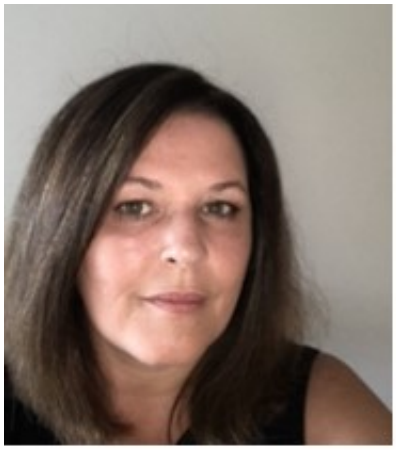
Abstract figure

The figure illustrates 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.

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Susan Joyce



Dr Susan Joyce is a lecturer and a principal investigator interested in metabolism and in metabolites produced by microbes that influence host responses, among them bile acids and fatty acids. She applies microbial and cellular molecular approaches combined with mass spectrometry applications and clinical investigations to her scientific questions. Her group enjoys research funding from Science foundation Ireland, Department of Food and Marine, EU and Government of Irish Research Council.

Dervla O'Malley



Dr Dervla O'Malley is a lecturer and principal investigator with a research focus on neuro-endocrine regulation of gut function and the physiological mechanisms underlying gastrointestinal dysfunction. Using imaging and electrophysiological techniques, her research team aims to elucidate and understand how luminal factors, including bile acids, signal across the gut barrier to the peripheral and central nervous systems.

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