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Contributions of bile acids to gastrointestinal physiology as receptor agonists and modifiers of ion channels

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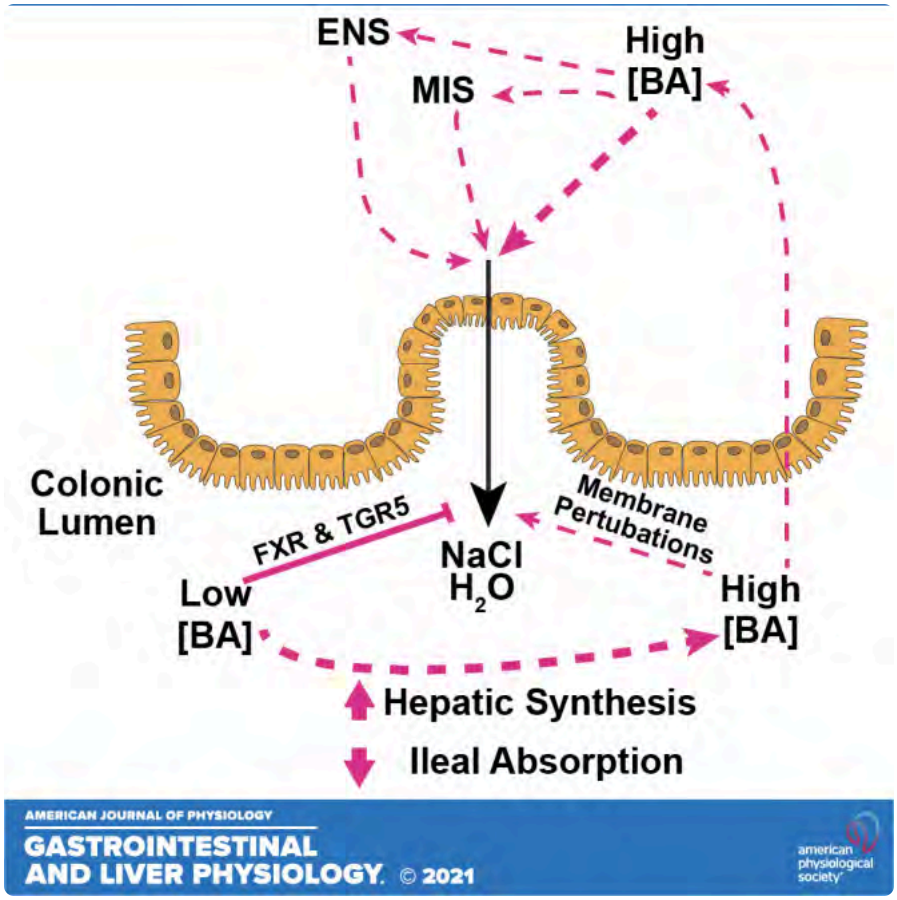

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Abstract

Bile acids (BAs) are known to be important regulators of intestinal motility and epithelial fluid and electrolyte transport. Over the past two decades, significant advances in identifying and characterizing the receptors, transporters, and ion channels targeted by BAs have led to exciting new insights into the molecular mechanisms involved in these processes. Our appreciation of BAs, their receptors, and BA-modulated ion channels as potential targets for the development of new approaches to treat intestinal motility and transport disorders is increasing. In the current review, we aim to summarize recent advances in our knowledge of the different BA receptors and BA-modulated ion channels present in the gastrointestinal system. We discuss how they regulate motility and epithelial transport, their roles in pathogenesis, and their therapeutic potential in a range of gastrointestinal diseases.

INTRODUCTION

Bile acids (BAs) are amphipathic steroidal molecules found as a major component of bile. BAs are synthesized in hepatocytes, stored in the gall bladder, and released into the small intestine in response to the ingestion of a meal. Classically, BAs are known for their roles in digestion through facilitating the solubilization of fatty acids, stimulating bile flow and intestinal motility, regulating glucose levels, and promoting cholesterol secretion and catabolism (1). BAs modulate their own

synthesis, transport, and detoxification and aid in the maintenance of a healthy gut microbiome. Primary BAs, such as cholic acid (CA) and chenodeoxycholic acid (CDCA), are synthesized in the liver and the vast majority are conjugated (e.g., tauro-CA or glyco-CA) before their release into the ileum. In the terminal ileum, ~95% of released BAs are reabsorbed through the ileal BA transporter, IBAT (also known as apical sodium-dependent BA transporter, ASBT). BAs that are not reabsorbed in the ileum enter the colon where they undergo structural modifications catalyzed by anaerobic bacterial enzymes, such as 7α-dehydroxylase, to become secondary BAs (e.g., deoxycholic acid, DCA and lithocholic acid, LCA) (2).

Normally, the BAs are reabsorbed in the terminal ileum and are recycled back to the liver via the enterohepatic circulation. However, disruptions to the enterohepatic circulation, whether due to increased BA synthesis or defective re-uptake in the small intestine, results in BA accumulation in the colon. When present at physiological levels, BAs act as important signaling molecules that exert their actions through specific receptors located on the cell surface and in the nucleus. However, given their amphipathic nature and detergent-like properties, increased levels of BAs in the colon can have deleterious effects on the lipid composition of cellular membranes in this region and exert cytotoxic and membranolytic effects (3, 4). Given the detergent-like properties of BAs, caution must be taken when interpreting studies where high concentrations of exogenous BAs have been used. Unless specifically assessed, any observed effects may be attributable to deleterious effects of BAs on the lipid composition of cellular membranes, receptor-mediated effects, or a combination of the two. In this review, we aim to summarize recent advances in the field of BA signaling in the gut with a particular emphasis on how they regulate transport function and motility, and consideration of the effects of physiological versus pathophysiological concentrations of BAs.

BILE ACID RECEPTORS

The discovery that BAs can act as transmitters and mediate cellular signaling processes has been a significant advancement to our understanding of how they exert their functional effects. BAs selectively activate a broad range of G protein-coupled receptors (GPCRs), nuclear receptors, and ion channels. Strategies that indirectly alter their actions at these sites are already used to treat a range of conditions. For example, modulation of luminal BA levels, either through sequestration or altered transport, is currently the main therapeutic approach to treat BA-associated disorders, such as cholestatic itch or gallstones. However, the potential for directly targeting BA-activated receptors and ion channels now offers additional opportunities for therapy. This review provides a summary of GPCRs, nuclear receptors, and ion channels that are influenced by BAs. It aims to contextualize how the distribution, functions, and regulation of BA receptors relate to gastrointestinal (GI) physiology and how their dysregulation is implicated in digestive disease and disorders.

BILE ACID INTERACTION WITH G PROTEIN-COUPLED RECEPTORS

GPCRs are dynamic signaling proteins that are mainly located on the cell surface. They enable cells to detect and respond to a diverse array of extracellular ligands and stimuli. It is now known that BAs can activate several distinct GPCRs, including established bona fide BA receptors (Takeda G protein-coupled receptor 5, TGR5), receptors that interact with BAs in addition to their primary

orthosteric agonists (e.g., muscarinic receptors), and putative BA receptors (e.g., Mrgprs). A summary of the current findings is provided in Table 1, with a more detailed description listed in the following sections.

Takeda G Protein-Coupled Receptor 5

TGR5, also known as bile acid receptor, GPBA, GpBAR1, or M-BAR1 is activated by both primary and secondary BAs. TGR5 is G_s-coupled meaning activation of the receptor stimulates adenylyl cyclase to produce cAMP. TGR5 is expressed by a diverse range of cell types in tissues including, but not limited to, gastrointestinal, liver, brown adipose, skeletal muscle, and placental. Within the gastrointestinal tract, TGR5 is expressed by epithelia, enteroendocrine cell subsets, enteric neurons, enteric glia, smooth muscle, monocytes/macrophages, and extrinsic afferents (6, 27). The roles of TGR5 in intestinal motility and secretion will be discussed in detail throughout this review. TGR5 has additional signaling roles in many other gastrointestinal processes that have not been discussed here including inflammation and the development of cancers, and visceral pain (6, 28).

Mas-Related G Protein-Coupled Receptor X4

Mrgprs are a family of orphan GPCRs consisting of more than 50 members. There are several subfamilies, with mouse and human receptors characterized separately. For example, sensory neurons in the dorsal root ganglia (DRG) of mice express MRGPRA1, whereas the ortholog Mas-related G protein-coupled receptor X4 (MRGPRX4) is expressed in human tissues (29). Their contributions to sensation have not been fully characterized, but roles in nociception and itch have been identified. In patients with the gall bladder condition, primary biliary cholangitis, elevated levels of blood BAs are known to cause the symptom of cholestatic itch and BA sequestrants or IBAT inhibitors are used to treat the condition. However, when studying BA activation of the MRGPR family of receptors, interpretation of results may be complicated by differences in the responses of the mouse and human orthologs. For example, recent evidence from in vivo studies in transgenic mice indicates that BA-induced itch is not dependent on the expression of several Mrgprs. Mice lacking a cluster of Mrgpr genes (Mrgpr-cluster$^{-/-}$) exhibit itch in response to DCA in a similar manner to control mice (30). HEK cells transfected with the mouse ortholog MRGPRA1 do not respond to BAs as measured by Ca^{2+} signaling. In contrast, cells expressing the human MRGPRX4 are activated by BAs, and this is the only human receptor to respond (11). Similarly, mice expressing the humanized receptor demonstrate a greater itch response following acute injection of DCA or ursodeoxycholic acid (UDCA) compared with control mice. This same study showed that control mice responded comparably to both BAs, and this is evidence that a Mrgpr-mediated response may not involve activation of TGR5, since UDCA is a poor agonist for the latter receptor (11). It should be noted that longer administration of UDCA is used to treat pruritus associated with cholestasis, with suggested benefits such as stimulation of biliary BA excretion, replacement of the toxic endogenous BA pool, and stabilization of plasma membranes and cytoprotection of cholangiocytes (31).

In the context of the digestive system, the expression of Mrgprs has been described predominantly in primary afferent DRG neurons innervating the intestine. However, some studies have characterized mRNA expression in healthy or inflamed GI tissues. More specifically, expressions of

MrgA4, MrgB2, MrgB8, MrgE, and MrgF have been demonstrated by immunohistochemistry in neurochemically defined subsets of enteric neurons (32–35). Activation of Mrgprs in cells such as mast cells could in turn activate closely associated primary afferent and sensory neurons through release of mediators including histamine and proteases. Mrgprs can interact with other cell surface receptors, such as transient receptor potential (TRP) channels to promote cellular responses (36). The relative importance of these interactions in the context of other BA-activated receptors and ion channels is not known. There are populations of primary afferent neurons innervating the gut wall that coexpress Mrgprs and TGR5. Given that both receptors are involved in histamine-independent itch pathways in the skin, this has led some researchers to postulate their function as a visceral "irritant sensing system," suggesting their contribution to pain and symptomology in irritable bowel syndrome (IBS) (6). In a recent study in mice by Castro et al., chronic visceral hypersensitivity (CVH) responses to colorectal distention were induced by intraluminal application of DCA, and agonists of MRGPRA3 and MRGPRC11. Whether DCA was acting on Mrgpr receptors was not studied here. Although the expression profiles of TGR5, MRGPRA3, and MRGPRC11 were identified in mouse sensory DRG neurons, expression of MRGPRA1 was not mentioned. The same study examined the response profiles of human DRG neurons. Although they found that cells responded to TGR5-preferring agonists they did not study receptor specificity for these responses and this may be due to limitations in the pharmacological tools currently available. The expression profiles of MRGPRX4 were also not mentioned (6).

Muscarinic Acetylcholine Receptors

Some BAs can interact with muscarinic receptors to influence cholinergic signaling. This is likely the result of structural similarities between some BAs and acetylcholine (ACh), as has been identified for lithocholic acid conjugates (37, 38). Secondary BAs, including taurolithocholic acid (t-LCA), block cholinergic-induced contractions of mouse and human airway smooth muscle evoked by either exogenous ACh or by electrical stimulation of parasympathetic nerve terminals, possibly by acting as antagonists of M3 muscarinic receptors (14). Urso et al. found that this was not through specific activation of TGR5, as BAs continued to relax preconstricted smooth muscle tissues from *tgr5*$^{-/-}$ mice, and selective TGR5 small molecule agonists did not relax tissue from wild-type animals. A role for BAs in muscarinic signaling is further supported by studies in cardiomyocytes, where taurocholate inhibited cAMP-production in a pertussis toxin-sensitive manner to limit contraction. This response was prevented upon pharmacological inhibition or siRNA knockdown of the M2 muscarinic receptor (12, 13). Muscarinic receptors have prominent roles in gastrointestinal motility and secretion. Therefore, it is surprising that not more is known about the implications of BAs interacting with muscarinic receptors in these processes.

Sphingosine-1-Phosphate Receptor 2

Sphingosine-1-phosphate receptor 2 (S1PR2) is one of a series of receptors that respond to the bioactive lipid mediator, lysosphingolipid (S1P). S1PRs are ubiquitously expressed in different tissues and this is reflected by their roles in many processes including angiogenesis, lymphangiogenesis, cell proliferation and motility, immune cell function, and lipid metabolism (39). S1PR2 also has a role as a BA receptor (40). In GPCR screening assays, rodent hepatocytes responded to BAs through extracellular signal-regulated kinase (ERK)1/2 and protein kinase B/Akt signaling. These

BA-mediated responses were reduced by an S1PR2-selective antagonist, knockdown of the receptor, and using cells from S1PR2 knockout mice (15). Furthermore, the proliferation of cholangiocytes and onset of liver fibrosis in response to experimental bile duct ligation were attenuated in S1PR2-deficient mice, consistent with the proposed interaction of S1PR2 and BAs (16).

Formyl Peptide Receptors

Formyl peptide receptors (FPRs) are a group of GPCRs involved in innate immune responses. *N*-Formyl-methionyl-leucyl-phenylalanine (fMLP), a major chemotactic factor, is an agonist with different binding affinities for the three FPRs. fMLP binds with high- and low affinities to formyl peptide receptor (FPR) and formyl peptide receptor-like type-1 (FPRL-1), respectively. However, formyl peptide receptor-like type-2 (FPRL-2) does not bind to *N*-formyl peptides. Roles for FPRs in BA-induced signaling have been demonstrated in studies on human monocytes and using human embryonic kidney cells (HEK-293) transfected with FPR and FPRL-1. In these cells, pretreatment with CDCA and DCA inhibited fMLP binding to its receptors and associated elevations in intracellular Ca^{2+} (17, 18). In these same studies, cell migration stimulated by fMLP was inhibited by CDCA and DCA treatment (17, 18). Although these studies did not assess whether TGR5 mediates BA-dependent inhibition of chemotaxis and calcium signaling in these cells, computational modeling experiments have demonstrated antagonist binding sites for DCA on the FPR (41), supporting the idea that direct inhibition of these BA receptors is involved. Intestinal microbiota are known to produce fMLP, and recent studies of interactions between the microbiome, FPRs, and gut motility suggest that FPR-expressing enteric neurons are important mediators of probiotic-induced gut motility (42). It is therefore plausible that BAs could modulate gastrointestinal physiology through actions on neuronal FPRs. However, direct experimental evidence for such interactions is currently lacking. Furthermore, since FPRs are also expressed by intestinal neutrophils with different expression patterns noted for cells isolated from tissues of patients with Crohn's disease (43), BA/FPR interactions on intestinal immune cells could have important implications for pathogenesis of inflammatory bowel diseases (IBDs).

NUCLEAR RECEPTORS FOR BILE ACIDS

Nuclear receptors are a family of ligand-activated transcription factors, comprised of a ligand-binding domain and a DNA-binding domain to promote or suppress transcription. Activators for these receptors include steroid hormones such as estrogen and progesterone and lipid-soluble mediators such as retinoic acid and vitamin D. In this way they allow factors such as hormones or nutrients to modulate gene expression (44). BAs are ligands for several nuclear receptors with roles in glucose, lipid, and energy metabolism (45). These receptors regulate BA levels in the enterohepatic circulation and mediate processes in inflammation. They represent novel targets for a range of therapies for metabolic, cholestatic liver, and inflammatory bowel diseases (46, 47).

Farnesoid X Receptor

Farnesol was originally thought to be the cognate ligand for farnesoid X receptor (FXR), but this agonist only activates the receptor at supraphysiological concentrations (48). In contrast, conjugated and unconjugated BAs activate FXR at physiological levels with CDCA being one of the most potent agonists (19, 20, 49). FXR is highly expressed in liver and intestinal tissues and has significant roles in mediating both metabolic processes and BA homeostasis. Studies of FXR knockout mice provide evidence for the roles of FXR-dependent BA metabolism, as these mice have elevated levels of circulating BAs and they excrete fewer BAs in their fecal matter (50). In hepatocytes, FXR activation limits the production of primary BAs by various pathways that include downregulating the rate-limiting enzyme for BA synthesis. It also stimulates the secretion of BA from the liver into the gall bladder and limits hepatic reuptake. In intestinal cells, FXR activation promotes downstream pathways that lead to intracellular transport of BAs and reduce BA production in hepatocytes (45, 51). In human ileal enterocytes, BA-mediated activation of FXR stimulates transcription of the hormone fibroblast growth factor 19 (FGF-19, mouse ortholog FGF-15) (21, 22). FGF-19/FGF-15 then activates a downstream pathway in hepatocytes, ultimately inhibiting the production of BAs (45). Maintaining BA homeostasis is important for liver function but when improperly regulated can lead to a range of digestive diseases. For example, BA-diarrhea (BAD) is thought to be caused by alterations in enterohepatic circulation. Given the roles of FXR in stimulating these processes, FXR agonists have been successfully tested for their therapeutic potential to treat this condition (51, 52). The therapeutic potential may extend beyond regulating the enterohepatic circulation of BAs since activation of FXR has been shown to promote antisecretory effects in colonic epithelial cells (53). These additional roles are discussed in more detail later in this review (see BILE ACIDS AND INTESTINAL TRANSPORT OF ELECTROLYTES AND FLUID). In the liver, FXR activation also limits glucogenesis and lipogenesis, therefore, targeting FXR has potential as a therapeutic strategy to treat a range of metabolic conditions, such as nonalcoholic steatohepatitis (54, 55).

Pregnane X Receptor

A range of lipophilic chemicals bind to Pregnane X receptor (PXR) including xenobiotics, endogenous hormones, and BAs (56). PXR is responsible for the metabolism, detoxification, and elimination of such agents. It is highly expressed in the liver and small intestine (24). PXR activation enhances the production of enzymes responsible for BA metabolism/detoxification, represses enzymes involved in BA synthesis, and alters the expression of BA transport proteins (23, 24, 57). LCA also activates PXR (24, 57). Along with FXR, targeting PXR has been proposed as a possible IBD treatment, particularly for patients with Crohn's disease associated with BA-diarrhea [BAD (58)]. In patients with BAD, the activities of enzymes that catalyze BA metabolism are reduced, enzymes that facilitate BA synthesis are elevated and hence the balance of BAs levels is dysregulated. These studies have postulated that PXR or FXR may be deactivated in these patients (59, 60). Dextran sulfate sodium (DSS)-induced colitis is more severe in PXR knockout mice when compared with the wild-type control, and activation of PXR can alleviate the development of inflammation in wild-type mice (61).

Vitamin D Receptor

Typically, vitamin D receptor (VDR) responds to the active form of vitamin D, 1α,25-dihydroxyvitamin D3 $1,25(OH)_2D_3$. The receptor is expressed in the intestine and kidneys where it mediates a range of processes such as calcium homeostasis, cellular differentiation, and immunity.

LCA is a metabolite of CDCA. Although the primary BAs, CDCA and CA, do not activate VDR, LCA is a potent VDR agonist (25). Oral administration of LCA to mice can induce the expression of some of the same targets genes as VDR activation by $1,25(OH)_2D_3$ (26). Although clarity on the physiological relevance for LCA activation of VDR is lacking, it is thought to have a protective role by mediating the elimination and breakdown of LCA, given the cytotoxic and pro-oncogenic nature of the BA (62, 63). Since, intestinal bacteria metabolize CDCA to LCA, it is hypothesized that this provides a mechanism for intestinal bacteria to regulate host VDR function. Recent evidence suggests that the LCA-VDR interactions may have protective roles for the intestinal epithelial barrier (64). This is supported by observations that VDR knockout mice develop dextran sulfate sodium (DSS) colitis more quickly and robustly than wild-type animals (65), and in patients with Crohn's disease or ulcerative colitis colonic epithelial VDR expression is reduced (66).

LCA acts on FXR, PXR, and VDR to modulate BA metabolism, and the downstream effects of these interactions regulate the activities of the cytochrome P450 (CYP) family of enzymes (45). These enzymes protect the body from a variety of lipophilic chemicals, such as BAs, and their actions are controlled at a transcriptional level by many different signaling molecules. Activation of VDR, by either LCA or $1,25(OH)_2D_3$, induces transcription of the CYP3A4 gene (25). The CYP3A4 enzyme assists in the detoxification of LCA and other BAs by catalyzing their hydroxylation. Hydroxylation of BAs means they are more hydrophilic, facilitating their excretion in fecal matter or urine. The importance of this interaction is demonstrated in VDR knockout mice, where intestinal, circulating, and fecal BA pools are all dysregulated (65, 67). Insertion of the CYP3A4 gene into these mutant mice improves the BA pool size so that the relative levels of BAs in liver and intestine homogenates return to levels comparable with those of wild-type mice. It also reduces the effects of LCA-induced toxicity by stimulating LCA metabolism (68).

Constitutive Androstane Receptor

Constitutive androstane receptor (CAR) is expressed in the liver and intestines where it mediates the detoxification of phenobarbital-like inducers (69). Although endogenous activators for CAR are not well characterized, both androstenol and androstanol have been identified as repressive endogenous ligands for constitutive activity. BAs are unlikely to directly activate CAR (70) but indirect activation has been suggested in LCA-induced liver toxicity models. CAR knockout mice develop more severe damage compared with wild-type controls, highlighting that LCA detoxification could not occur in these mice (71). CAR expression is reduced in the colon from mice with DSS-induced colitis. Similarly, mucosal intestinal biopsies from patients with Crohns' disease and ulcerative colitis also have reduced CAR expression when compared with healthy individuals (72).

FXR, PXR, and CAR regulate overlapping target genes in BA metabolism. To investigate how they coordinate their activities, several studies have used double knockout mice for different combinations of these receptors. They suggest that the receptors jointly protect against BA-induced liver toxicity (71, 73, 74). The gut microbiome regulates the function and expression of CAR and PXR

receptors by stimulating the conversion of primary BAs to secondary BAs. Tissues from germ-free (GF) mice express significantly lower mRNA levels for CAR, PXR, and FXR as well as for a range of cytochrome P450 enzymes relative to mice housed under specific pathogen-free (SPF) conditions (75). In conventional mice, daily administration of CAR and PXR agonists changes the biodiversity of their microbiome by reducing two taxa in the *Bifidobacterium* genus (76). Again, this highlights the potential interplay between the gut microbiome, the regulation of BAs levels, the expression this group of receptors, and their activation by BAs.

BILE ACIDS AS MODIFIERS OF ION CHANNEL ACTIVITY

BAs can also exert their effects through interactions with ion channels. Specific ionotropic receptors for BAs have not been identified to date. However, there is good evidence that BAs can modulate the functions of several members of the epithelial sodium channel/degenerin (ENaC/DEG) family. This interaction may be physiologically relevant in tissues where BAs have access to these channels, such as in the intestine and bile ducts. The regulation of these channels by hormones and local factors is highly complex and involves the regulation of channel expression, trafficking, and open probability. Several members of the ENaC/DEG family of ion channels can qualify as ligand-gated ion channels. These include the acid sensing ion channels (ASICs) and the FMRFamide-activated Na^+ channel (FaNaC) that are activated by protons and the tetrapeptide FMRFamide, respectively. For other members of this family, no specific activating ligands have been described with the possible exception of BA-sensitive ion channel (BASIC). A summary of the actions of BAs on ion channels and ionotropic receptors is provided in Table 2.

BA-Sensitive Ion Channel

BA-sensitive ion channel (BASIC) is a member of the ENaC/DEG ion channel family (previously known as intestinal Na^+ channel (INaC) in humans or brain-liver-intestine Na^+ channel (BLINaC) in rodents) (94, 95). BASIC is expressed on the apical membrane of rat cholangiocytes (77, 80). It shows very low basal activity in heterologous expression systems, but is strongly activated by submillimolar concentrations of BAs (77–82). Based on this observation, it is possible that BAs may act as endogenous ligands for the channel in tissues where they are present at high concentrations, such as the bile ducts and the small intestine. However, the stimulatory effect of BA on BASIC does not seem to be as potent and as specific as the stimulatory effect of ligands on classical ionotropic receptors. Moreover, a modulatory effect of BAs on ion channel activity does not seem to be limited to BASIC.

Epithelial Sodium Channel

Epithelial sodium channel (ENaC) is expressed in the apical membrane of epithelia in a range of tissues, including the distal colon and the biliary ducts (96). It mediates transepithelial sodium absorption and therefore regulates fluid volume (97–100). Recent evidence suggests that BA sensitivity is not a unique feature of BASIC but may be a common feature of channels belonging to the

ENaC/DEG family. Similar or lower concentrations of BAs needed to activate BASIC can stimulate the rat, mouse, and human ENaC (83–85). Generally, BAs activate ENaC with varying abilities, but some also inhibit the channel (84–86).

It is likely that exposure of ENaC to changing levels of BAs in cholangiocytes and distal colon may modify the function of the channel under physiological conditions. In kidney and distal colon, ENaC plays an important role in mediating sodium absorption. In these tissues, ENaC is mainly stimulated by the mineralocorticoid aldosterone but can also be regulated by additional mediators and local mechanisms (101–104).

Despite the location of ENaC on the apical membrane, BAs may also affect the channel through interactions originating from the basal surface. Preliminary studies demonstrated that LCA applied to the serosal side of the mouse distal colon had a sustained stimulatory effect on ENaC-mediated transepithelial Na^+ transport. This is reminiscent of the stimulatory effect of aldosterone (105). The delayed and sustained stimulatory effect of LCA on ENaC may be due to transcriptional regulation involving a nuclear receptor, such as FXR. A dual stimulatory effect of BAs on ENaC from the apical and basolateral side may serve as a compensatory mechanism in the colon to limit fluid loss during diarrhea resulting from impaired ileal BA absorption (for a more detailed discussion of the effects of BA on intestinal transport see BILE ACIDS AND INTESTINAL TRANSPORT OF ELECTROLYTES AND FLUID).

Human Acid-Sensing Ion Channel ASIC1a

ASIC1a is another member of the ENaC/DEG family of ion channels. Although BAs do not directly activate ASIC1a, they positively modulate proton-activated ASIC1a currents (87). BAs may not act as classical ligands on the orthosteric site of the channel, but rather modulate the function of already active ASIC1a channels by interacting with a topographically distinct, allosteric site. Using site-directed mutagenesis and computer simulation it has been shown that BAs may directly interact with the transmembrane domains of ENaC/DEG ion channels in the so-called “degenerin region” known to be functionally important for channel gating (81, 84, 87). BA binding to the transmembrane domains of the channel probably stabilizes the channel open conformation leading to increased channel activity. Several ASICs are responsible for distinct proton-gated currents in neurons regulating gastrointestinal function (106). Thus, it is tempting to speculate that modulation of ASICs by BAs may contribute to gastrointestinal physiology and pathophysiology.

Other Ion Channels and Ionotropic Receptors

BA may also modulate other ion channels and ionotropic receptors. For example, BAs have been shown to modify the function of large-conductance Ca^{2+}- and voltage-activated K^+ (BK) channels via distinct channel subunits and sites (88), they also inhibit currents mediated by ionotropic NMDA and $GABA_A$ receptors (89–91). Recently, it has been demonstrated that the human purinergic receptor $P2X_4$, an ATP-gated nonselective cation channel, is inhibited by unconjugated or tauro-conjugated DCA (92). The inhibitory effect of BAs is not limited to $P2X_4$ and has also been reported for the related $P2X_2$ receptor (93). A comparison of the crystal structure of $P2X_4$ revealed a high degree of similarity in topology and architecture with that of ASIC1 (107), suggesting

structural similarities of their BA binding sites. Indeed, tauro-DCA probably interacts with the transmembrane domains of $P2X_4$ thereby stabilizing its closed state (92). $P2X_4$ is abundantly expressed in hepatocytes and cholangiocytes (108, 109) and $P2X_2$ is present in gall bladder and enteric neurons (110, 111). Therefore, BAs may potentially play a role as local modulators of purinoceptors in these systems.

BILE ACIDS AND INTESTINAL TRANSPORT OF ELECTROLYTES AND FLUID

Bile Acids Modulate Intestinal Fluid and Electrolyte Transport in Pathophysiology

Intestinal fluid absorption is critical for effective homeostatic control of whole body fluid and electrolyte balance. Na^+ absorption drives fluid uptake across small intestinal villi and surface cells of the colon, whereas Cl^- secretion drives fluid secretion occurring mainly from the crypts. Three main mechanisms drive Na^+ absorption along the gut as follows: while digestion is occurring, small intestinal Na^+-nutrient co-transporters predominate; during the interdigestive period, Na^+/H^+ exchange predominates along the entire length of the intestine; and electrogenic Na^+ absorption is the primary mechanism driving fluid absorption in the distal colon (112). Depending on physiological versus pathophysiological conditions, BAs can activate both proabsorptive and prosecretory pathways to influence ion flux and water retention.

There has long been an association between increased luminal BA levels and the onset of diarrhea in humans. However, the roles of BAs in fluid dysregulation were not recognized until much later than their effects on intestinal motility (see BILE ACIDS AND INTESTINAL MOTILITY). The first preclinical demonstration of such actions came in 1966, where perfusion of DCA, at a concentration of 100 μM, to the rat jejunum inhibited intestinal fluid absorption (113). Based on observations in patients with ileitis and increased BA turnover, Hofmann (114) proposed that the increased levels of luminal BAs were causing the clinical symptoms of diarrhea. This hypothesis was subsequently supported by clinical studies showing that direct administration of dihydroxy BAs to the colorectum induced diarrhea in healthy individuals (115), whereas infusion of conjugated and unconjugated BAs inhibited jejunal water absorption (116).

Typically, only dihydroxy BAs (e.g., DCA and CDCA) alter epithelial transport processes and, in humans, diarrhea only occurs when BAs are present at pathophysiological levels (see Table 3). In the small intestine where their uptake to enterohepatic circulation can occur via IBAT, conjugates of DCA and CDCA exert similar actions to their nonconjugated counterparts but with lower potency. However, in the colon there is a lack of apical uptake pathways and therefore luminal conjugated BAs cannot enter the epithelium unless the barrier becomes compromised, as occurs in conditions of intestinal inflammation. Conjugated BAs can then gain access to the basolateral domain and enter the epithelial cell via basolateral transporters to stimulate increases in free cytosolic Ca^2 (for more details see *Molecular Mechanisms of Bile Acid-Induced Fluid Transport*), thereby activating intracellular mechanisms that promote fluid secretion and inhibit absorption (133, 134). Interestingly, unlike the other dihydroxy BAs, UDCA does not stimulate fluid secretion in the colon and appears to exert antisecretory actions when it is present at sufficiently high levels (135).

Molecular Mechanisms of Bile Acid-Induced Fluid Transport

BAs induce luminal fluid accumulation by inhibiting Na^+ absorption and promoting Cl^- secretion in both the small intestine and colon. This has been demonstrated in many animal models using in vitro and in vivo methods to assess fluid and ion transport in the ileum (136–139) and colon (140, 141). Studies using cultured intestinal epithelial cell lines and on isolated human colonic crypts have provided considerable insights into mechanisms by which BAs induce luminal fluid accumulation and diarrhea. In Caco-2 cells, a model of absorptive epithelial cells, conjugated BAs inhibit Cl^-/OH^- exchange (142). Likewise, when present at high concentrations, CDCA inhibits both Na^+/H^+ exchange (NHE) activity and Cl^-/HCO_3^- exchange in isolated human colonic crypts (143). As discussed in BILE ACIDS AS MODIFIERS OF ION CHANNEL ACTIVITY, BAs can also modify the function of ENaC, which plays a role in Na^+ absorption in the distal colon, particularly when plasma aldosterone levels are increased to minimize renal and intestinal sodium losses. High concentrations of BAs can rapidly induce Cl^- secretion from the crypts across both small intestinal and colonic epithelial cells. This effect appears to involve activation of basolateral K^+ channels, where K^+ leaving the cells provides the electrochemical driving force for Cl^- to exit through channels in the apical membrane. This most likely occurs through the cystic fibrosis transmembrane conductance regulator (CFTR) (144).

The actions of BAs on these transport proteins appear to be predominantly mediated by elevations in intracellular Ca^{2+} (133, 143, 145). BAs have been shown to induce increases in intracellular Ca^{2+} by both influx across the plasma membrane and release from the endoplasmic reticulum (143, 146, 147). However, the upstream mechanisms leading to increased intracellular Ca^{2+} are still not well defined. The fact that only dihydroxy BAs are active might point to the involvement of a receptor. However, neither TGR5, which appears to exert antisecretory actions (7, 148), nor the nuclear receptor, FXR, is a likely candidate. As noted previously in this review, BAs have detergent-like properties and by inducing perturbations in the cell membrane, this may lead to activation of downstream signaling pathways, thereby promoting their prosecretory and antiabsorptive actions (149, 150). It appears that BAs can also directly interact with endoplasmic reticulum membranes to increase cytosolic Ca^{2+} levels (151, 152).

It is clear from studies of isolated epithelial cells that BAs can exert direct actions on intestinal absorption and secretion. However, studies from ex vivo tissues demonstrate that BAs acting on other mucosal cells may also contribute to this dysregulation. As discussed in *Actions of Bile Acids on the Mucosa to Promote Colonic Motility*, luminal BAs can stimulate enterochromaffin cells (ECC) within the mucosa to release serotonin (5-HT). 5-HT can then activate enteric neural pathways, including those that regulate fluid secretion (153–155). Such neural pathways may provide a mechanism by which changes in intestinal fluid and electrolyte transport can be coordinated with changes in motility and permeability (5, 156–158). BAs can also activate mucosal mast cells to release their mediators (159), most notably histamine, and this may be important in mediating Cl^- secretory responses to CDCA (160). It is also important to note that mast cells and enteric nerves exist close to one another in the intestinal mucosa and that interactions between these two cell types are likely to be important in regulating epithelial transport responses to BAs (161, 162).

Roles of Bile Acids in Epithelial Fluid and Electrolyte Transport under Physiological Conditions

In contrast to their acute prosecretory and antiabsorptive effects at high concentrations, BAs have recently been shown to exert antisecretory actions at more physiologically relevant levels (53, 105, 163). Such antisecretory effects are slow in onset (12–24 h) and for DCA occur at concentrations as low as 50 μM, a concentration that is well within the normal physiological range for this BA in the proximal colon (164). Such antisecretory actions of naturally occurring BAs are mimicked by selective FXR agonists and are associated with reduced expression and activity of basolateral Na^+-K^+-ATPase pumps and apical CFTR Cl^- channels (53). We have proposed that under such physiological conditions, BAs may function to inhibit colonic fluid secretion, thereby promoting the normal absorptive function of the colon (summarized in Fig. 1). Thus, by virtue of their opposing actions at low versus high concentrations, dihydroxy BAs may have the capacity to dynamically control the fluidity of the luminal contents. In this context, bacterially mediated deconjugation of luminal BAs would be essential to permit their entry into the cell where FXR activation can occur to induce antisecretory actions. Thus, diet or disease-associated changes in the colonic microbiota that result in altered expression of bile salt hydrolase activity could have important implications for fluid and electrolyte transport (165–169).

Studies have also investigated the potential role for TGR5 in regulating colonic fluid and electrolyte transport. These revealed that TGR5 also exerts antisecretory effects, although its role appears to be distinct to that of FXR. Treatment of muscle-stripped, nerve-free, mucosal preparations of rat colon with the TGR5-selective agonist, INT-777, rapidly and transiently reduced basal Cl^- secretion with a concomitant inhibition in the capacity of the tissue to evoke secretory responses to Ca^{2+}-dependent secretagogues (148). Furthermore, the effects of INT-777 were mimicked by LCA, an endogenous ligand for TGR5. Subsequent studies revealed that TGR5 activation may also dampen colonic Cl^- secretion by inhibiting submucosal neurons. Such actions are proposed to represent a regulatory mechanism that may counterbalance BA-induced fluid secretion (7). A schematic representation of the roles of BAs in regulating colonic intestinal fluid and electrolyte transport is depicted in Fig. 1.

BILE ACIDS AND INTESTINAL MOTILITY

There is strong, consistent evidence that oral delivery or rectal administration of BAs promotes colonic motility. Although early experimental evidence from in vivo studies in rabbit demonstrated that luminal infusion of secondary BAs promotes colonic motility (131, 132), the most compelling evidence comes from clinical studies (124–126). Rectal perfusion of CDCA to healthy individuals reduces the perceived defecatory urge and enhances the frequency of distension-evoked pressure waves or bowel movements (124, 127). Similarly, oral administration of CDCA significantly accelerates colonic transit, but not gastric emptying or colon filling (125). These effects are not limited to healthy patients since in individuals with constipation, oral administration of BAs increases stool frequency and decreases stool consistency (126, 170). This work highlights the therapeutic potential of targeting BA signaling to treat gastrointestinal motility disorders. A summary of the roles of BAs in GI motility and the relative concentrations required to stimulate these actions is presented in Table 3.

Mechanisms for the Prokinetic Actions of BA and the Case for TGR5

Early literature from clinical studies implicates the role of TGR5 in the prokinetic actions of BAs in the colon. Results from clinical trials testing the efficacy of UDCA and CDCA to dissolve and treat gallstones demonstrated that patients treated with CDCA, but not UDCA, experienced diarrhea as a side effect (123, 171, 172). Furthermore, constipation was relieved by treatment with CDCA, but not UDCA (123). This may be explained by the differing agonist activities of the BAs at TGR5, where UDCA has a lower efficacy and potency for TGR5 agonism than CDCA (9, 173). This aligns with evidence from candidate genotype analysis using PCR-based methods, where TGR5 genotype variations are associated with constipation and diarrhea in patients with IBS (174, 175).

Although selective TGR5 agonists are becoming available, the functional effects of TGR5-selective drugs on colonic motility in humans have not yet been investigated. However, studies in mice and dogs demonstrate that TGR5 is expressed throughout the gastrointestinal tract in enteric neurons, epithelial and enteroendocrine cells, and smooth muscle. TGR5 has been identified as a regulator of colonic motility in these species under normal conditions (5, 128, 176). Indeed, there are likely several mechanisms by which BAs can modulate intestinal motility. Data from in vitro studies suggest that BAs exert prokinetic actions when exposure is limited to the mucosa (5), but exposure to the muscularis externa inhibits intestinal motility (128). In the latter case, BAs may have a direct action on the smooth muscle cells to impair contractile activity (130, 177), or may directly activate inhibitory enteric motor neurons that express TGR5 (128). Such inhibitory actions of BAs on the muscularis externa do not contradict the findings from clinical studies. The absence of transporters, such as ASBT, that permit the absorption of conjugated BAs in the colon limits their access to this tissue layer (178), and most clinical studies involve BA exposure to the gut lumen. Therefore, it is likely that the prokinetic actions of BAs are due to effects initiated in the mucosa. Direct effects of BAs on the muscularis externa may be more relevant in disease conditions, such as inflammation, where loss of barrier function and increased paracellular permeability allows both conjugated and unconjugated BAs to passively pass through the mucosa (179, 180).

Actions of Bile Acids on the Mucosa to Promote Colonic Motility

BAs promote the release of several bioactive mediators from the intestinal mucosa. For example, isolated human ECC release 5-HT following exposure to sodium deoxycholate (57), while mucosal application of BAs to rat jejunum (153) and mouse colon promotes 5-HT release possibly via a TGR5-dependent mechanism (5). This BA-mediated 5-HT release activates neural pathways to promote peristaltic contractions (5).

In addition to 5-HT, it is well documented that BAs also stimulate intestinal L cells to release the peptide hormones glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) (119, 181–185). This involves TGR5-dependent and TGR5-independent mechanisms (8, 9, 186, 187). The release of GLP-1 and PYY is important for regulating appetite and metabolism. One mechanism of action of GLP-1 in metabolism is to promote insulin release, and hence GLP-1 receptor agonists are used clinically to treat diabetes mellitus. GLP-1 and PYY promote digestion and nutrient absorption by delaying gastric emptying and reducing intestinal motility. Infusion of BAs to the lumen of the stomach and small intestine in vivo reduces gastric emptying and intestinal transit in the rat, rabbit, and human (117, 118, 120, 121). The association between BAs, the release of neuropeptides, and delayed

small intestinal motility is supported by studies in the rabbit ileum (122) and human stomach (119), where luminal perfusion of BAs increases the plasma concentrations of PYY or GLP-1, respectively, and this is associated with reduced GI motility in these regions.

BAs mediate opposing effects on motility of the small versus large intestines and it is unclear whether neuropeptide release alone can account for these differences. Rectal administration of tauro-CA in humans dose-dependently increases plasma GLP-1 and PYY levels (127, 182) and this is associated with increased defecation frequency (127). GLP-1 or PYY may directly regulate the BA-mediated changes in motility and this could explain the differential actions in the upper gut and colon where they are present at differing concentrations. In vitro studies show that application of GLP-1 inhibits the responses of intestinal muscle strips to electrical stimulation or exogenous application of ACh without influencing basal tone. This inhibition is likely due to an action on enteric inhibitory neurons (188–190), but also involves actions on the smooth muscle cells themselves (189). Myenteric and submucosal neurons functionally express GLP-1 receptors. In studies on wholemount preparations of rat colon, application of the highly selective agonist, exendin-4, stimulated increases in intracellular calcium in a proportion of neurons from both regions (191). In vivo motility studies indicate that regulation from the central nervous system may also be involved (191, 192). There is conflicting data as to whether PYY stimulates (193, 194) or inhibits GI smooth muscle contractility (195, 196) and these effects may be region-specific (197, 198). PYY is a 36-amino acid polypeptide that is endogenously expressed as either full-length PYY1-36 or as the truncated PYY3-36 form. These peptides have different affinities for the Y receptors that PYY targets (199). Therefore, the presence and activity of PYY variants may account for differences in the contractile responses of different regions to PYY. The cell surface enzyme, dipeptidyl peptidase IV (DPP-IV), both inactivates GLP-1 and converts PYY from its long to its truncated form. Thus, the activity of DPP-IV may play a significant role in shaping the contractile responses to PYY and GLP-1 following BA activation. GLP-1 containing L-cells are evenly distributed across the stomach, small intestine, and colon. In contrast, PYY containing L-cells typically populate the distal small intestine and colon only (195, 200, 201). Whether TGR5 is equivalently expressed by all L-cells regardless of if they contain PYY or GLP-1 remains to be determined, and how these profiles may also contribute to the generation of gut motility patterns is also unknown.

Differing results using taurine-conjugated versus unconjugated isoforms and the use of individual BAs versus mixtures of BAs provide better insight on how they influence motility (see Table 3). In a study by Brown et al. (118), perfusion of the ileum with taurocholic acid (tauro-CA) increased stomach to caecum transit time. In contrast, this transit time decreased with perfusion of DCA. Ullmer et al. found that taurine-conjugated and unconjugated BAs have an equal binding affinity for human-TGR5 in cell lines. However, their effectiveness to increase plasma PYY levels in animals depended on systemic versus luminal application of the agonists (10). The taurine-conjugated TGR5 agonist tauro-RO5527239 did not stimulate secretion of PYY from L-cells, whereas the unconjugated form did. Conjugated forms of BAs or TGR5 agonists have limited ability to access the receptor that is located on the basal side of epithelial cells (186). We speculate that this, in turn, would limit the release of factors, such as PYY, by these cells and thus potentially limit their influence on intestinal motility. Given the importance of the colonic microbiome in determining BA deconjugation, it is clear that changes in bacterial populations that express bile salt hydrolases are

likely to significantly impact how BAs modulate fecal transit through the colon. (166–169). BA modulation by the colonic microbiome may therefore be influenced by factors such as diet modification or the onset of disease.

Bile Acids and Intestinal Motility Disorders

Enhanced delivery of BAs to the colon has long been associated with diarrhea (114, 202), with ~25%–33% of patients with chronic functional diarrhea having increased BA delivery to the colon (203). In some rare cases, BA-malabsorption (BAM) can be due to loss-of-function mutations in intestinal bile acid transporters, such as ASBT and organic solute transporter β (Ostβ) (5, 204–206). However, BAM is most commonly due to structural damage brought about by ileal inflammation from conditions such as Crohn's disease, or following surgical or radiation procedures (207–209). Idiopathic BAM is characterized by increased delivery of BAs in the stool in the absence of structural pathology. Alterations in BA synthesis (174, 210–212) or the enterohepatic circulation (213) are attributed as the causes of BAM and the resultant diarrhea in these conditions. Moreover, studies suggest that 10%–26% of patients with diarrhea predominant IBS (IBS-D) may have BAM as the underlying cause (214). Conversely, recent evidence suggests that some instances of constipation may result from reduced BA delivery to the colon. In a retrospective study, Vijayvargiya et al. (215) reported that 15% of patients with IBS-C had decreased fecal BA levels compared with healthy control patients (45 patients, 108 controls). This evidence for the important roles of BAs in a range of GI motility conditions has prompted research into the therapeutic potential of altering BA delivery to the colon or influencing BA receptor signaling.

More recent clinical studies have shifted away from the direct administration of BAs to patients, to investigating the therapeutic potential of modulating the delivery of endogenous BAs. This approach has produced results consistent with the effects of exogenous administration of BAs. One such strategy is to inhibit the reuptake of BAs in the terminal ileum, using drugs such as IBAT inhibitor, Elobixibat (A3309) (216–218). In vivo studies in constipated dogs (218) and clinical trials conducted in Europe, North America, and Japan have all demonstrated Elobixibat to effectively increase the number of spontaneous bowel movements and to improve stool consistency in patients with chronic constipation (219–222). Elobixibat is now an approved drug for the treatment of constipation in Japan (223). There is limited knowledge as to whether administration of ASBT inhibitors can promote GI motility under control conditions (i.e., nonconstipated patients). However, in vivo experiments in dogs demonstrated that Elobixibat induced giant migrating contractions and increased defecation frequency and fecal wet weight within 10 h of administration (224).

Several other IBAT inhibitors, including volixibat, maralixibat, odevixibat (A4250), and GSK2330672 are in various stages of clinical trials to treat conditions such as nonalcoholic steatohepatitis (225), type 2 diabetes mellitus (226), and cholestatic pruritus in primary biliary cholangitis (227–231). In all of these studies, diarrhea and abdominal pain are cited as treatment-related adverse events, with an incidence ranging from 10% to 80%. Although it is unclear whether a patient subtype is more or less likely to develop these symptoms, the dosage of the drugs can be correlated with the number of reported incidences. Recently published results of a phase 2 clinical trial for GSK2330672 to treat cholestatic pruritus reported diarrhea as an adverse event in 38%, 65%, and 66% of patients receiving 20, 90, and 180 mg of the drug, respectively. This was com-

pared with 11% of patients receiving the placebo (229). This highlights the importance of establishing efficacy, safety, and tolerability of these drugs to treat these conditions. As noted elsewhere, BAs will cause symptoms such as diarrhea when delivered at high, pathophysiological concentrations; therefore, it would be interesting to know how the levels of fecal BAs correlated with symptom severity. In healthy volunteers, volixibat increased fecal BAs by 1.6–3.2 times compared with those that had received placebo. It is worth noting that there was no clear correlation between dosage of volixibat (0.5–5 mg) and excreted BAs. How these levels correlated with symptom severity was not reported. However, these results highlight that there may be variability in the ways in which patients respond to these drugs.

Another approach to modulating endogenous levels of BAs involves the use of BA sequestrants that have opposing effects to ASBT inhibitors and reduce free BA levels in the colon. Such drugs, which include cholestyramine and colesevelam, have been trialed to treat a range of diarrhea-associated conditions including idiopathic BA-diarrhea and BA-associated diarrhea in Crohn's disease and IBS-D (57, 125, 217, 232–234). As FXR activation leads to the inhibition of BA production in hepatocytes, FXR agonists have also been trialed to treat BA-induced diarrhea (52, 86, 235). Two small clinical trials conducted in the UK and the USA have demonstrated the benefits of the FXR agonists obeticholic acid and tropifexor. Daily tropifexor administration had a small but significant effect on slowing ascending colonic motility in patients with primary BA-diarrhea in a recent safety profiling study [60 μg daily, n = 8 (235)]. Obeticholic acid given to patients with primary BA-diarrhea improved stool frequency and formation during a 2-wk treatment period [25 mg, daily, n = 10 (52)]. However, patients with chronic idiopathic diarrhea did not have improved symptoms (n = 8) indicating that neither FXR activation nor limiting physiological levels of BA production have roles in controlling colonic motility (52). This differs to patients with BA-diarrhea, where removing excess BAs reduces the symptoms of the disease. It is important to note that GI motility and secretion are interlinked, where increasing secretion will stimulate motility. FXR agonists limit intestinal fluid secretion in mouse models of secretory diarrhea (53). However, these studies did not specifically study direct GI motor indices.

When considering the potential for targeting BAs for therapeutic purposes, it is important to consider how the gut microbiome interacts with these molecules and their receptors to modulate intestinal motility (236). There is a growing appreciation for the roles of intestinal bacteria in a range of GI disorders. BAs increase intestinal permeability, providing greater opportunity for microbiota to access the gut wall. Although the BAs can modulate motility directly, the inflammation promoted by the infiltrating bacteria can also alter intestinal motility (237). This pairs with the proposed role of TGR5 in regulating intestinal inflammation, which may involve TGR5 expressing-circulating macrophages (179, 180). Recent studies in mice have highlighted that with age-related changes to the microbiome there is an increase in fecal deconjugated BAs. TGR5 activation by conjugated BAs in young mice stimulated an anti-inflammatory phenotype in muscularis macrophages (mMac) protecting normal motility. With aging, the shift of fecal BA content to deconjugated BAs led to reduced TGR5 activation. This resulted in a phenotypic switch of mMac to a more proinflammatory state, stimulating low-grade inflammation in these tissues and thus delayed GI transit (238). The microbiome-BA balance and its role in intestinal motility seem an obvious considera-

tion when trying to understand complex treatment strategies such as fecal transplants (236). This could have important implications for our understanding of the pathology of a range of GI motility disorders but may also provide novel therapeutic strategies for these conditions.

CONCLUSION

The BA receptor axis is a viable therapeutic target, as evidenced by the clinical use of BA sequestrants and more recently IBAT inhibitors. With the discovery of specific BA receptors, BA-modulated ion channels, and BA transporters, our understanding of the roles of BAs in physiological processes and disease has evolved. BAs have physiological actions as signaling molecules through binding and activation of both cell surface and nuclear receptors and through modifying ion channel function. They also drive pathophysiological changes in disease and may have mechanistic roles in GI disorders including IBS. As outlined in this review, there remains the need for greater understanding of the functional importance of BA receptors, particularly those which have only recently been defined.

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AUTHOR CONTRIBUTIONS

S.E.C. analyzed data; D.P.P. and S.E.C. prepared figures; S.J.K., A.U., A.V.I., C.K., N.W.B., D.P.P., and S.E.C. drafted manuscript; S.J.K., A.U., A.V.I., C.K., N.W.B., D.P.P., and S.E.C. edited and revised manuscript; S.J.K., A.U., A.V.I., C.K., N.W.B., D.P.P., and S.E.C. approved final version of manuscript.

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Figures and Tables

Table 1.

Effects of BAs on G protein-coupled receptors and nuclear receptors

Receptor	Bile Acid	Concentration	Tissue Preparation	Response	Effect	Solvent	Refs.
			G protein-coupled receptors				
TGR5 (GPR130, GpBAR1)	DCA OA	1–100 μM 100 μM	Proximal colon from *tgr5*-WT and KO mice	↑ WT KO only 100 μM at DCA	5-HT and CGRP from EC cells to stimulate peristaltic reflex	0.1% Ethanol, distilled water	(5)
	DCA TLCA CCDC	100 μM	DRG neurons innervating colon (mouse)	↑ ↑ ↑	Increased intracellular Ca^{2+} in subpopulations of neurons (%) DCA ~20%, TLCA~ 25%, CCDC~30%	NA	(6)
	CCDC	100 μM, 100 μL rectal enema	Spinal cord (mouse)	↑	Phosphorylated MAP-kinase-ERK-1/2 immunoreactivity (pERK-IR) enhanced in response to colorectal distention	Saline	
	INT-777	10–100 μM	Proximal colon (mouse)	↑	Increased transepithelial resistance and reduced short circuit current, reduced with TTX or neuron-free preparation	DMSO	(7)
	UDCA	3–60 μM		-	Weak TGR5 agonist		
	LCA, DCA	10 and 30 μM	Enteroendocrine	↑	Promote GLP-1	DMSO	(8)

CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; LCA, lithocholic acid. 3-Keto-LCA is the major metabolite of LCA in rats. UDCA, ursodeoxycholic acid; t-, tauro-conjugated; g-, glyco-conjugated bile acid. Cell lines: rat basophil leukemia cell line transfected with FPR EFTR cell; mouse large cholangiocytes MLE; monkey kidney CV-1 cells; human hepatoma HepG2; enteroendocrine cell line, STC-1. Responses: activation, ↑; inhibition, ↓; no change, -. Solvents: NA, no information available; DMSO stock, dimethyl sulfoxide (DMSO).

Table 2.

Effects of bile acids on ion channels and ionotropic receptors

Ion Channel	Bile Acid	Effect: Stimulation ↑ Inhibition ↓	Concentration Used or EC_{50}/IC_{50}, if Available	Solvent	Cells Expression System	Refs.
		Epithelial sodium channel/degenerin ion channel family				
$BASIC^{rat}$	g-CDCA, t-CDCA g-HDCA, t-HDCA	↑↑↑	1–1.5 mM g-HDCA: EC_{50} ~ 2 mM	NA	*X. laevis* oocytes	(77, 78)
	t-CA, t-βMCA	↑				
	UDCA	↑↑↑	EC_{50} ~ 2.5 mM			
	t-UDCA, t-HDCA	↑↑↑	1–2 mM t-UDCA: EC_{50} ~ 2.7 mM	NA	HEK293 cells	(79)
	t-CA, t-LCA t-DCA, t-CDCA	↑↑				
	t-CDCA, t-HDCA t-UDCA	↑↑	500 µM–1 mM	NA	Normal rat cholangiocytes (NRC)	(80)
$BASIC^{human}$	t-DCA	↑↑↑	500 µM–1 mM	Bath solution	*X. laevis* oocytes	(77, 81, 82)
	t-CDCA	↑↑↑		NA		
	t-CA, t-HDCA	↑				
	t-DCA, t-CDCA	↑↑↑	1–2 mM	NA	HEK293 cells	(79)
	t-CA, t-UDCA t-HDCA, t-LCA	↑				
$BASIC^{mouse}$	t-CA, t-UDCA, t-HDCA t-LCA, t-	↑↑	1–2 mM t-UDCA: EC_{50} ~ 4.5 mM	NA	HEK293 cells	(79)

CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; HDCA, hyodeoxycholic acid; LCA, lithocholic acid; UCA, ursocholic acid; UDCA, ursodeoxycholic acid; 12βHICA, 12β-hydroxyisocholic acid; βMCA, β-muricholic acid; t-, tauro-conjugated; g-, glyco-conjugated bile acid. Solvents: NA, no information available; bath solution, bile acids/bile salts were directly dissolved in bath solution to obtain the indicated final concentrations; DMSO stock, dimethyl sulfoxide

(DMSO) stock solutions were prepared with bile acids at a concentration of 100 mM; H_2O stock, aqueous stock solutions were prepared with bile acid concentrations ranging from 20 to 100 mM; DMSO/ethanol stock, concentrated dimethyl sulfoxide (DMSO) stock solutions were prepared with bile acids at a concentration of 333 mM and then further diluted 1/10 in 95% ethanol.

Table 3.

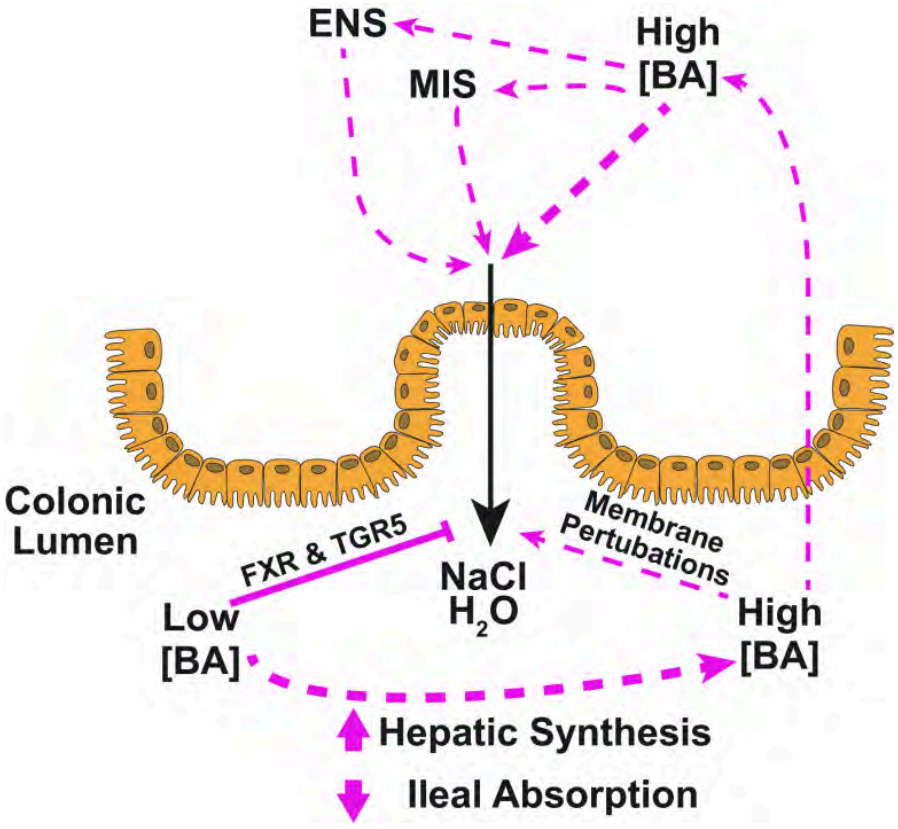
Effects of bile acids on gastrointestinal motility

GI Region/Application Method/ Measurement	Animal Species	Bile Acid	Concentration Used	Effect:	Refs.
Stomach and small intestine					
Stomach and small intestine/oral gavage/phenol red	Rat	t-DCA DCA	26–100 mM 5–26 mM	GE ↓ SIT ↓ GE ↓↓ IT ↓↓	(117)
Stomach-cecum/ileum infusion/environmental hydrogen analysis		t-CA DCA	10 mM 10 mM	SCTT ↑ SCTT ↓	(118)
Stomach/nasogastric/paracetamol absorption test	Human (healthy and type 2 diabetes)	CDCA	1.25 g in 100 mL water	GE ↓	(119)
Small intestine					
Jejunum and ileum/intraluminal infusion/lactulose and in vivo manometry	Human (healthy)	g-CDCA g-CA	15–30 mM 15 mM	SIT ↓ SIT ↓	(120, 121)
Terminal ileum/intraluminal infusion/ex vivo manometry	Rabbit	Rabbit bile t-DCA	0.1–10 mM	MA ↓ MA ↓ at 10 mM	(122)
Colon (in vivo)					
GI and colonic transit/oral/side effect profile	Human (cholesterol gallstone)	UDCA CDCA	7–8 and 14–15 mg/kg/day (3–12 mo)	BF – BF ↑	(123)
Proximal colon/ rectal perfusion/in vivo manometry and GI sensation	Human (healthy)	CDCA	1 mM	Sensory threshold ↓ PS ↑	(124)
GI and colonic transit/oral capsule/scintigraphy method and bowel function	Human (healthy and IBS-C)	CDCA	500, 1,000 mg	CT ↑ BF ↑	(125) (126)
GI and colonic transit/rectal perfusion/ GI sensation	Human (healthy)	TCA	1,500 and 3,500 mg	Sensory threshold ↓ BF ↑	(127)
Colon (in vitro/ex vivo)					
Colonic motility/bath addition muscle exposure/contraction assay	Mouse *tgr5-wt* and *ko*	UDCA DCA	100 μM 1, 10, 100 μM	WT contraction -	(128, 129)

CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; LCA, lithocholic acid; UDCA, ursodeoxycholic acid; t-, tauro-conjugated; g-, glyco-conjugated bile acid; Rank order of potency for TGR5 is t-LCA > LCA > DCA > CDCA, UDCA and OA are weak TGR5 agonists. Responses: stimulation, ↑; inhibition, ↓; no change, -. BF, bowel function; CT, colonic transit; GE,

gastric emptying; IBS-C, irritable bowel syndrome-constipation predominate; MA, motor activity; PR, peristaltic reflex; PS, propagating sequences; SIT, small intestinal transit.

Figure 1.



Bile acids (BAs) in regulation of colonic epithelial Cl^- secretion. BAs are normally present in the colon at relatively low concentrations where they act via BA receptors, such as Farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5), to inhibit salt and water secretion into the lumen (*left*). We propose that such actions serve to promote normal colonic absorptive function. In some pathological conditions, increased delivery of BAs to the colon may result from either increased synthesis of primary BAs by hepatocytes or reduced ileal absorption. The resulting high levels of luminal BAs induce perturbations in the epithelial cell membranes to promote Cl^- secretion and inhibit Na^+ absorption, thereby promoting luminal fluid accumulation (*right*). Such direct effects of BAs on the epithelium are amplified by indirect actions involving the release of neurotransmitters and mediators from the enteric nervous and mucosal immune systems (ENS and MIS, respectively). It is thought that, under such circumstances, increased colonic fluid secretion is a protective mechanism that serves to dilute the abnormally high levels of luminal BAs.