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Duodenal chemosensing

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Abstract

Purpose of review—Luminal chemosensing is a term used to describe how small molecules in the gut lumen interact with the host through surface receptors or via transport into the submucosa. In this review, we have summarized recent advances of understanding luminal chemosensing in the gastroduodenal mucosa, with a particular emphasis on how chemosensing affects mucosal protective responses and the metabolic syndrome.

Recent findings—In the past decade, data have supported the hypothesis that gut luminal chemosensing not only is important for the local or remote regulation of gut function but also contributes to the systemic regulation of metabolism, energy balance and food intake. We have provided examples of how luminal nutrients such as long-chain fatty acids (LCFAs), endogenous compounds such as bile acids, bacterial metabolites such as short-chain fatty acids (SCFAs) and bacterial components such as lipopolysaccharide (LPS) activate cognate receptors expressed on key effector cells such as enteroendocrine cells and inflammatory cells in order to profoundly affect organ function through the initiation or suppression of inflammatory pathways, altering gut barrier function and nutrient uptake, altering gut motility and visceral pain pathways, and preventing mucosal injury.

Summary—These recent discoveries in this area have provided new possibilities for identifying novel molecular targets for the treatment of mucosal injury, metabolic disorders and abnormal visceral sensation. Understanding luminal chemosensory mechanisms may help to identify novel molecular targets for the treatment and prevention of mucosal injury, metabolic disorders and abnormal visceral sensation.

Keywords

cholecystokinin; enteroendocrine cells; G protein coupled bile acid receptor 1; G protein coupled receptors; glucagon-like peptides; gut chemosensing; gut hormones; lipopolysaccharide; long-chain fatty acids; short-chain fatty acids

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INTRODUCTION

The duodenal mucosa is exposed to a mixture of semi-digested food, secreted acid and bacterial components and metabolites. As the most proximal intestinal segment, the duodenal mucosa has a unique chemosensory capacity that senses the luminal content, followed by the rapid release of bioactive mediators and hormones that have local and systemic effects [1]. The identification of luminal chemosensors in the gastrointestinal tract has emerged in the past decade in part from the de-orphanization and characterization of nutrient-sensing G protein coupled receptors (GPCRs) [1]. Gut luminal chemosensing is implicated not only in the local or remote regulation of gut function but also in the systemic regulation of metabolism, energy balance and food intake [1].

Gut physiological processes such as secretion, digestion, absorption and motility are affected by these luminal substances, in addition to central nervous control via vagal nerves initiated at the cephalic phase of food intake. The first discovery of gut hormone release in response to a luminal substance was secretin release in response to luminal hydrogen ion (H^+) concentration [1]. To date, ~20 gut hormones, principally localized in enteroendocrine cells (EECs) or myenteric neurons in the gastrointestinal tract have been identified. Extensive studies have clarified the contributions of these gut hormones in the regulation of gut function via GPCR activation as well as via food intake control through vagal afferent signals. Nevertheless, the mechanism underlying food-evoked gut hormone release is not well understood.

In this review, we will summarize recent reports addressing luminal chemosensing in the gastroduodenal mucosa with a focus on mucosal protective responses and metabolic syndrome.

LONG-CHAIN FATTY ACID SENSING

Long-chain fatty acids (LCFAs) and monoacylglycerol (MAG) generated from fat (triglyceride) digestion by pancreatic lipase are detected by the LCFA receptors free fatty acid (FFA)1 (GPR40) and FFA4 (GPR120), and the MAG receptor GPR119. Luminal LCFA and MAG increase the release of proglucagon products from enteroendocrine L cells such as glucagon-like peptide (GLP)-1 and GLP-2, gastric inhibitory polypeptide/glucose-dependent insulinotropic peptide (GIP) from K cells and cholecystokinin (CCK) from I cells [2–4,5■], suggesting that the corresponding receptors are expressed on L cells, K cells and I cells, respectively. Furthermore, LCFA-FFA1 mediated G_q-coupled intracellular Ca^{2+} increase with the MAG-GPR119-mediated G_s-coupled intracellular cAMP increase, synergistically increase GLP-1 release [6■].

As the fat enters duodenum, I cells in the intestine secrete CCK, often referred to as the archetypal gut hormone, a key intestinal peptide secreted by small intestinal EECs in response to ingested nutrients [7]. Digested luminal fats, LCFA and MAG are absorbed by enterocytes, mainly in the jejunum, via active and passive pathways. LCFA is partially absorbed via cluster-of-differentiation (CD) 36 mediated pathway [8]. A recent study shows that sulphated CCK-8 and GLP-2 increase LCFA uptake as N-oleoylethanolamide (OEA)

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via CCK1 receptor activation and upregulation of CD36 in primary cultures of mouse duodenocytes. [9]. Although genetic deletion of CD36 or fatty acid transport protein (FATP) isoforms has no effect on fat absorption [10,11], CD36 and FATP are important for LCFA transport *in vitro* [8,12], suggesting that these active transport molecules constitute a high-affinity, low capacity transport system. LCFA and MAG are re-esterified by diglyceride acyltransferase 1 (DGAT1) to triglyceride (triglyceride resynthesis), forming nascent chylomicrons after subsequent combination with apolipoprotein B-48. Chylomicrons are released by exocytosis from enterocytes into the central lacteals and villous lymphatic capillaries, draining into the mesenteric lymph ducts, followed by the thoracic duct into systemic circulation [13].

Interestingly, in a recent study that evaluated the expression of the fat sensors FFAR1, FFAR4, GPR119 and the LCFA sensor/transporter, CD36, in the human duodenum, GPR119 was identified to be an early transcriptional responder to duodenal lipid in lean humans, although this response appeared reduced in individuals with high polyunsaturated fatty acid (PUFA) intake [14]. These observations may have implications for downstream regulation of gut hormone secretion and appetite.

SHORT-CHAIN FATTY ACID SENSING

Short-chain fatty acids (SCFAs) are volatile fatty acids, including C2 (acetate), C3 (propionate), and C4 (butyrate), synthesized by the fermentation of dietary fibre and present in the lumen of the foregut in low concentrations compared with their principal location in the cecum and the proximal colon.

FFA2 and 3 are nutrient GPCRs with specific affinity for SCFAs [15]. In the rat duodenal mucosa, FFA2 is expressed in enterochromaffin cells containing 5-hydroxytryptamine (5-HT), whereas FFA3 is colocalized with glucagon-like peptide (GLP)-1 in L cells [16]. Duodenal loop perfusion revealed that luminal perfusion of a synthetic high-affinity selective FFA2 agonist increases the release of 5-HT from enterochromaffin cells and stimulates duodenal HCO_3^- secretion via activation of 5-HT_4 and muscarinic receptors [16]. A synthetic selective FFA3 agonist increases GLP-2 release from L cells, which activates GLP-2 receptors, increasing HCO_3^- secretion via the secondary release of vasoactive intestinal peptide (VIP) and nitric oxide [17■■,18]. The endogenous ligands acetate and propionate also stimulate HCO_3^- secretion via GLP-2 receptor activation, enhanced by the addition of a dipeptidyl peptidase 4 (DPP4) inhibitor, likely due to the prolongation of the serum $t_{1/2}$ of the DPP4 substrate GLP-2 [16].

GLP-2 release via FFA3 activation supports the therapeutic efficacy of synthetic FFA3 ligands on experimental nonsteroidal anti-inflammatory drug (NSAID)-induced enteropathy. Oral administration of a synthetic selective FFA3 agonist prevented the formation of NSAID-induced small intestinal ulcers associated with GLP-2 release [17■■]. As FFA3 is also functionally expressed on myenteric neurons, intraperitoneal or serosal treatment of a synthetic selective FFA3 agonist inhibited colonic motility and cholinergic ion secretion [19■■,20] but had no effect on NSAID-induced enteropathy [17■■]. These studies suggest

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that orally delivered FFA3 ligands may be a novel therapeutic for the prevention of NSAID-induced enteropathy.

In contrast, oral treatment with a selective FFA2 agonist, which increases 5-HT release from enterochromaffin cells, dose-dependently induced duodenal mucosal injury when coadministered with ulcerogenic doses of NSAIDs, a novel observation as NSAIDs usually do not injure the duodenum in rat models [21■■]. Duodenal mucosal injury is induced by gastric acid and 5-HT_3 receptor activation, accompanied by increased 5-HT release into the portal vein and impaired acid-induced hyperemia via 5-HT_3 receptor activation [21■■]. As protective mucosal blood flow, mucus secretion and HCO_3^- secretion are reduced by injurious doses of NSAIDs, these results suggest that ulcerogenic doses of NSAIDs with concomitant FFA2 activation are accompanied by excessive release of 5-HT that remarkably reduces duodenal mucosal protective mechanisms followed by duodenal mucosal injury, supported by the observation that intra-aortic administration of 5-HT increases duodenal blood flow at low doses, but decreases blood flow at high doses [21■■].

Irritable bowel syndrome (IBS) is an idiopathic condition characterized by altered bowel habits and abdominal pain. As IBS symptoms respond to 5-HT_3 antagonists, nonabsorbable antibiotics that reduce small-intestinal bacterial overgrowth (SIBO) and a diet depleted of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FOD-MAP)s, we have hypothesized that excess fermentation of foregut FODMAPs by SIBO generates high foregut SCFA concentrations, overactivating FFA2 receptors expressed on enterochromaffin cells, releasing 5-HT with consequent gut dysmotility and abdominal pain [21■■].

INTESTINAL ALKALINE PHOSPHATASE: SURFACE pH REGULATION AND LIPOPOLYSACCHARIDE DETOXIFICATION

Intestinal alkaline phosphatase (IAP) is a glycosylphosphatidylinositol (GPI)-anchored ectoenzyme highly expressed in the brush border membrane of duodenal epithelial cells [22]. As the optimal pH of IAP is 8–9 and IAP activity is closely correlated to the secretory rate of HCO_3^- [22], IAP may act as a surface pH sensor in the duodenum, maintaining extracellular pH homeostasis through a process we have termed ‘ectopurinergic signaling’. At neutral luminal pH, extracellular ATP nonlytically released from the epithelial cells is rapidly degraded to adenosine (ADO), which is further degraded to inosine by ADO deaminase. Once the surface pH is lowered by gastric acid, surface ATP concentrations increase due to the decreased degradation or the increased release of ATP, as IAP activity is reduced at acidic pH. Increased surface ATP concentrations activate purinergic P2Y receptors expressed on the apical membrane of epithelial cells, increasing the rate of HCO_3^- secretion. Increased surface [HCO_3^-] increases the surface pH, increasing IAP activity, which degrades surface ATP, terminating ATP-P2Y signalling. Luminal ADO additionally increases HCO_3^- secretion via adenosine A_{2B} receptors [23]. These studies suggest that IAP acts as a pH sensor to modify surface ATP concentrations, as part of a negative feedback loop. The mechanism of ATP-P2Y receptor signalling is implicated in other HCO_3^- secreting epithelia such as bile ducts, oviduct and bone [24].

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Lipopolysaccharide (LPS) is an endotoxin present in the outer coat of Gram-negative bacteria implicated in acute and chronic inflammation. Recent studies also demonstrate another important function of IAP in LPS detoxification, as IAP dephosphorylates the lipid A moiety of LPS [25], preventing activation of its cognate pro-inflammatory receptor Toll-like receptor 4 (TLR4) [26]. As exposure of the intestinal mucosa to LPS induces IAP gene expression, IAP activity is associated with decreased bowel inflammation. Decreased IAP expression is associated with increased LPS toxicity in zebrafish and intestinally derived Caco-2 cells [26–28]. Furthermore, IAP deficiency is associated with inflammation due to increased LPS toxicity in the human intestine [29] and in the intestines of vertebrate models in which IAP levels are decreased [28]. *In vivo*, however, the localization of IAP and LPS is mismatched, as IAP is expressed predominantly in the upper small intestine, duodenum and jejunum, whereas LPS is at highest concentrations in the ileum and colon due to the colonization of Gram-negative bacteria, the source of LPS [27]. One possible mechanism is that IAP cleaved from brush border membrane by phosphatidylinositol-specific phospholipase C (PI-PLC) is released into the lumen and reaches to ileum and colon, wherein it detoxifies LPS.

Gram-negative bacteria are present in oral flora. LPS often abundantly contaminates many foodstuffs [30], LPS is resistant to gastric acid and rodents are coprophagic, suggesting that foregut LPS exposure may occur. Excessive LPS exposure to the upper small intestine that exceeds the capacity of IAP-mediated detoxification may be transported through the mucosa, activating TLR4 expressed on epithelial cells and inflammatory cells, implicated in the pathogenesis of metabolic endotoxemia and inflammation (See ‘LPS transport’ below). Interestingly, oral administration of bovine IAP improves the metabolic syndrome induced by a high-fat diet [31], impairs the development of experimental colitis [32] and reduces alcoholic hepatosteatosis [33■], suggesting that IAP detoxification reduces the pro-inflammatory effects of LPS.

BILE ACID RECEPTOR TAKEDA G-PROTEIN-COUPLED RECEPTOR 5

In addition to lipids, bile acids also affect gut hormone release. Bile acids are the natural ligands for the GPCR, G protein-coupled bile acid receptor 1 (GBAR1, also known as Takeda GPCR 5 (TGR5) and the nuclear farnesoid X receptor (FXR), which are key regulators of energy and glucose homeostasis [34]. Activation of TGR5 by bile acids increases intracellular cyclic adenosine monophosphate (cAMP) levels, with subsequent suppression of cytokine production in macrophages [35]. Increased cAMP induced by forskolin and isobutylmethlyxanthine (IBMX) increases the release of GLP-1 from L cells [36], but the major link between luminal bile acids and GLP-1 release is probably mediated by TGR5 located on the L cell basolateral membrane [37]. The action of bile acids on GLP-1 secretion is principally mediated by TGR5 located on the basolateral L-cell membrane, suggesting that gut hormone release may be in response to absorbed receptor ligands [37]. Although TGR5 agonists increase GLP-1 release from the endocrine cell line STC-1 and the ileum of TGR5 transgenic mice [38,39], a TGR5 agonist alone has a little effect *in vivo* on GLP-1 release [39]. Nevertheless, DPP4 inhibition enhances serum GLP-1 concentrations in the presence of luminal TGR5 agonists and glucose, abolished in TGR5 knockout mice [39]. These results suggest that the bile acid induced TGR5 activation is a

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positive enhancer of glucose-induced GLP-1 release. TGR5 activation also decreases the production of pro-inflammatory cytokines in response to LPS via inverse modulation of the nuclear factor (NF)-κB signalling pathway [40].

TGR5 has also been implicated in duodenal mucosal protection through the increased rate of duodenal HCO_3^- secretion in response to luminal TGR5 ligands via the GLP-2 pathway [41]. Enhanced GLP-2 release in the presence of bile acids via TGR5 may be implicated in the adaptive mucosal repair that occurs after postprandial villous loss during food digestion. Furthermore, as GLP-2 has potent intestinotrophic and barrier-strengthening effects [42], TGR5 ligands may have beneficial effects on multiple diseases attributed to intestinal atrophy and increased intestinal permeability.

LUMINAL VERSUS BASOLATERAL NUTRIENT SENSING

Luminal nutrients are sensed by the cognate nutrient GPCRs expressed on EECs [43], generally believed to localize to the apical surface of enterocytes. Yet, the membrane localization of nutrient GPCRs has not yet been fully identified by immunohistochemistry. It is possible, however, that nutrients absorbed by adjacent epithelial cells are sensed by basolaterally expressed nutrient GPCRs expressed on EECs. Recent studies support this possibility: chylomicron synthesis and secretion are required for lipid-induced release of GIP and GLP-1 *in vivo*, consistent with lipid absorption followed by basolateral FFA receptor activation [44]; a vascularly but not luminally perfused FFA1 agonist increased GLP-1 release in the *ex vivo* small intestine [45]; chylomicrons increase GLP-1 release from $GLUT_{ag}$ cells via lipoprotein lipase and FFA1-dependent pathways, but not a GPR119-independent pathway [46■]. These studies suggest that LCFAs are sensed by basolateral FFA1 after LCFA absorption followed by chylomicron release, rather than by luminal LCFA sensing by apical FFA1. L cell density is greater in the hindgut (ileum and colon) than in the foregut (duodenum and jejunum). GPR119-dependent GLP-1 release is greater from colonic L cells than from upper intestinal L cells; lipid-induced GLP-1 release is abolished in L cell-specific GPR119 knockout mice [5■], suggesting that lipid-induced GPR119-dependent GLP-1 release principally originates from colonic L cells, which are not exposed to lipid in the lumen, but are possibly exposed to lipid at the vascular side after absorption. Alternatively, a vagal cholinergic reflex originating from the upper intestine to lower intestinal L cells may release GLP-1 during fat absorption [47].

The bile acid GPCR TGR5 is also functionally located on the basolateral membrane of L cells [37] as mentioned above. The TGR5 agonist taurodeoxycholate (TDCA) increases GLP-1 release from intestinal tissues when applied basolaterally or vascularly more than when applied luminally. Furthermore, the apical sodium-coupled bile acid transporter (ASBT) inhibitor abolishes luminal TDCA-induced GLP-1 release, suggesting that the absorbed bile acids stimulate the basolateral TGR5 on L cells prior to releasing GLP-1. These data suggest that the membrane localization of nutrient GPCRs may affect the therapeutic strategy used to target luminal or basolateral GPCRs by nonabsorbable or absorbable agonists or antagonists.

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LIPOPOLYSACCHARIDE TRANSPORT

Circulating LPS increases the permeability of the gut mucosal barrier, increasing LPS translocation into the circulation, augmenting endotoxemia with consequent systemic inflammation [48]. Increased serum LPS concentrations are associated with the metabolic syndrome, termed metabolic endotoxemia [49]. LPS aggravates low-grade inflammation [48], high-fat meals acutely increase circulating LPS levels in human healthy volunteers [50] and LPS appears in chylomicron remnants in mice [51], suggesting that luminal LPS physiologically crosses the gut barrier during fat absorption. Our recent studies demonstrate that luminal LPS is transported during fat absorption via lipid raft and CD36-mediated transcellular transport mechanisms, as studied in Ussing chambered jejunum *in vitro* and intestinal perfusion with cannulation of portal vein and lymph duct *in vivo* [52]. Exogenous GLP-2 also reduces LPS transport into the portal vein, suggesting that GLP-2 treatment may be a novel therapy for metabolic endotoxemia [52]. We have also observed that acute administration of GLP-2 reduces LPS-related increased intestinal permeability by a mechanism unlikely to be related to the known hypertrophic and hyperproliferative effects of chronic GLP-2 administration [53]. Therefore, exogenous GLP-2 treatment may be of value in the prevention of systemic inflammation associated with endotoxemia due to a ‘leaky gut’ [53].

CONCLUSION

Luminal chemosensors expressed on the epithelial cells populating the upper gastrointestinal tract communicate sensory information to effector systems involved in secretion, digestion, absorption, and motility as well as enhancing mucosal defense mechanisms through defined signalling mechanisms. Recent discoveries in this area have provided new possibilities for identifying novel molecular targets for the treatment of mucosal injury, metabolic disorders, and abnormal visceral sensation. Continued investigation of gut chemosensory mechanisms has the potential to inform the development of novel therapeutics for the treatments of diseases ranging from IBS and NSAID enteropathy to the metabolic syndrome.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

VA Author Manuscript VA Author Manuscript VA Author Manuscript

1. Akiba Y, Kaunitz JD. Duodenal luminal chemosensing; acid, ATP, and nutrients. Curr Pharm Des 2014; 20:2760–2765. [PubMed: 23886391]

2. Akiba Y, Kaunitz JD. Duodenal chemosensing: master control for epigastric sensation? J Gastroenterol Hepatol 2011; 26:6–7.

3. Hirasawa A, Tsumaya K, Awaji T, et al. Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. Nat Med 2005; 11:90–94. [PubMed: 15619630]

4. Iwasaki K, Harada N, Sasaki K, et al. Freefatty acid receptorGPR120 is highly expressed in enteroendocrine K cells of the upper small intestine and has a critical role in GIP secretion after fat ingestion. Endocrinology 2015; 156: 837–846. [PubMed: 25535828]

5■. Moss CE, Glass LL, Diakogiannaki E, et al. Lipid derivatives activate GPR119 and trigger GLP-1 secretion in primary murine L-cells. Peptides 2016; 77:16–20. [PubMed: 26144594] This study highlighted how GPR119 expressed on colonic L-cells in oral lipid-triggered GLP-1 secretion in vivo.

6■. Ekberg JH, Hauge M, Kristensen LV, et al. GPR119, a major enteroendocrine sensor of dietary triglyceride metabolites coacting in synergy with FFA1 (GPR40). Endocrinology 2016; 157:4561–4569. [PubMed: 27779915] The authors reported that that GPR119 is a primary component of the incretin response to triglycerides. Furthermore, GPR119 and FFA1 act synergistically to stimulate GLP-1 secretion.

7. Rehfeld JF. Cholecystokinin:from local gut hormone to ubiquitous messenger. Front Endocrinol (Lausanne) 2017; 8:47. [PubMed: 28450850]

8. Nassir F, Wilson B, Han X, et al. CD36 is important for fatty acid and cholesterol uptake by the proximal but not distal intestine. J Biol Chem 2007; 282:19493–19501. [PubMed: 17507371]

9. Demenis C, McLaughlin J, Smith CP. Sulfated cholecystokinin-8 promotes cd36-mediated fatty acid uptake into primary mouse duodenal enterocytes. Front Physiol 2017; 8:660. [PubMed: 28919867]

10. Goudriaan JR, Dahlmans VE, Febbraio M, et al. Intestinal lipid absorption is not affected in CD36 deficient mice. Mol Cell Biochem 2002; 239: 199–202. [PubMed: 12479586]

11. Shim J, Moulson CL, Newberry EP, et al. Fatty acid transport protein 4 is dispensable for intestinal lipid absorption in mice. J Lipid Res 2009; 50:491–500. [PubMed: 18843142]

12. Stahl A, Hirsch DJ, Gimeno RE, et al. Identification of the major intestinal fatty acid transport protein. Mol Cell 1999; 4:299–308. [PubMed: 10518211]

13. Tso P, Balint JA. Formation and transport of chylomicrons by enterocytes to the lymphatics. Am J Physiol Liver Physiol 1986; 250:G715–G726.

14. Cvijanovic N, Isaacs NJ, Rayner CK, et al. Duodenal fatty acid sensor and transporter expression following acute fat exposure in healthy lean humans. Clin Nutr 2017; 36:564–569. [PubMed: 26926575]

15. Brown AJ, Goldsworthy SM, Barnes AA, et al. The orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. J Biol Chem 2003; 278:11312–11319. [PubMed: 12496283]

16. Akiba Y, Inoue T, Kaji I, et al. Short-chain fatty acid sensing in rat duodenum. J Physiol 2015; 593:585–599. [PubMed: 25433076]

17■■. Said H, Akiba Y, Narimatsu K, et al. FFA3 activation stimulates duodenal bicarbonate secretion and prevents NSAID-induced enteropathy via the GLP-2 pathway in rats. Dig Dis Sci 2017; 62:1944–1952. [PubMed: 28523577] This study reported that duodenal luminal perfusion with a synthetic high-affinity FFA3 selective agonist increased GLP-2 release into the portal vein, enhancing mucosal protective mechanisms in vivo.

18. Wang J-H, Inoue T, Higashiyama M, et al. Umami receptor activation increases duodenal bicarbonate secretion via glucagon-like peptide-2 release in rats. J Pharmacol Exp Ther 2011; 339:464–473. [PubMed: 21846840]

19■■. Kaji I, Akiba Y, Furuyama T, et al. Free fatty acid receptor 3 activation suppresses neurogenic motility in rat proximal colon. Neurogastroenterol Motil 2018; 30:e13157.This study aimed to clarify how activation of neurally expressed FFA3 affects colonic motor function in an exogenous serotonin-induced defecation model.

VA Author Manuscript VA Author Manuscript VA Author Manuscript

20. Kaji I, Akiba Y, Konno K, et al. Neural FFA3 activation inversely regulates anion secretion evoked by nicotinic ACh receptor activation in rat proximal colon. J Physiol 2016; 594:3339–3352. [PubMed: 26854275]

21■■. Akiba Y, Maruta K, Narimatsu K, et al. FFA2 activation combined with ulcerogenic COX inhibition induces duodenal mucosal injury via the 5-HT pathway in rats. Am J Physiol Liver Physiol 2017; 313:G117–G128.Using an in vivo duodenal loop perfusion system, the authors measured portal vein serotonin concentrations, mucosal blood flow and duodenal bicarbonate secretion in response to perfusion with an FFA2 agonist, showing that in rats, FFA2 expression is primarily on enterochromaffin cells.

22. Akiba Y, Mizumori M, Guth PH, et al. Duodenal brush border intestinal alkaline phosphatase activity affects bicarbonate secretion in rats. Am J Physiol Liver Physiol 2007; 293:G1223–G1233.

23. Ham M, Mizumori M, Watanabe C, et al. Endogenous luminal surface adenosine signaling regulates duodenal bicarbonate secretion in rats. J Pharmacol Exp Ther 2010; 335:607–613. [PubMed: 20805305]

24. Kaunitz JD, Akiba Y. Purinergic regulation of duodenal surface pH and ATP concentration: Implications for mucosal defense, lipid uptake, and cystic fibrosis. Acta Physiol 2011; 201:109–116.

25. Bentala H, Verweij WR, Huizinga-Van der Vlag A, et al. Removal of phosphate from lipid A as a strategy to detoxify lipopolysaccharide. Shock 2002; 18:561–566. [PubMed: 12462566]

26. Vaishnava S, Hooper LV. Alkaline phosphatase: keeping the peace at the gut epithelial surface. Cell Host Microbe 2007; 2:365–367. [PubMed: 18078687]

27. Nakano T, Inoue I, Alpers DH, et al. Role of lysophosphatidylcholine in brush-border intestinal alkaline phosphatase release and restoration. Am J Physiol Liver Physiol 2009; 297:G207–G214.

28. Bates JM, Akerlund J, Mittge E, Guillemin K. Intestinal alkaline phosphatase detoxifies lipopolysaccharide and prevents inflammation in zebrafish in response to the gut microbiota. Cell Host Microbe 2007; 2:371–382. [PubMed: 18078689]

29. Tuin A, Poelstra K, De Jager-Krikken A, et al. Role of alkaline phosphatase in colitis in man and rats. Gut 2009; 58:379–387. [PubMed: 18852260]

30. Erridge C The capacity of foodstuffs to induce innate immune activation of human monocytes *in vitro* is dependent on food content of stimulants of Toll-like receptors 2 and 4. Br J Nutr 2011; 105:15–23. [PubMed: 20849668]

31. Kaliannan K, Hamarneh SR, Economopoulos KP, et al. Intestinal alkaline phosphatase prevents metabolic syndrome in mice. Proc Natl Acad Sci U S A 2013; 110:7003–7008. [PubMed: 23569246]

32. Ramasamy S, Nguyen DD, Eston M, et al. Intestinal alkaline phosphatase has beneficial effects in mouse models of chronic colitis. Inflamm Bowel Dis 2011; 17:532–542. [PubMed: 20645323]

33■. Hamarneh SR, Kim B, Kaliannan K, et al. Intestinal alkaline phosphatase attenuates alcohol-induced hepatosteatosis in mice. Dig Dis Sci 2017; 62:2021–2034. [PubMed: 28424943] IAP treatment attenuated the development of alcohol-induced fatty liver, lowered hepatic pro-inflammatory cytokine and serum LPS levels, and prevented alcohol-induced gut barrier dysfunction in mice.

34. van Nierop FS, Scheltema MJ, Eggink HM, et al. Clinical relevance of the bile acid receptor TGR5 in metabolism. Lancet Diabetes Endocrinol 2017; 5:224–233. [PubMed: 27639537]

35. Kawamata Y, Fujii R, Hosoya M, et al. A G protein-coupled receptor responsive to bile acids. J Biol Chem 2003; 278:9435–9440. [PubMed: 12524422]

36. Liou AP, Lu X, Sei Y, et al. The G-protein-coupled receptor GPR40 directly mediates Long-chain fatty acid-induced secretion of cholecystokinin. Gastroenterology 2011; 140:903–912. [PubMed: 20955703]

37. Brighton CA, Rievaj J, Kuhre RE, et al. Bile acids trigger GLP-1 release predominantly by accessing basolaterally located G protein-coupled bile acid receptors. Endocrinology 2015; 156:3961–3970. [PubMed: 26280129]

38. Katsuma S, Hirasawa A, Tsujimoto G. Bile acids promote glucagon-like peptide-1 secretion through TGR5 in a murine enteroendocrine cell line STC-1. Biochem Biophys Res Commun 2005; 329:386–390. [PubMed: 15721318]

VA Author Manuscript VA Author Manuscript VA Author Manuscript

39. Thomas C, Gioiello A, Noriega L, et al. TGR5-mediated bile acid sensing controls glucose homeostasis. Cell Metab 2009; 10:167–177. [PubMed: 19723493]
40. Duboc H, Tache Y, Hofmann AF. The bile acid TGR5 membrane receptor: from basic research to clinical application. Dig Liver Dis 2014; 46:302–312. [PubMed: 24411485]
41. Inoue T, Wang J-H, Higashiyama M, et al. Dipeptidyl peptidase IV inhibition potentiates amino acid- and bile acid-induced bicarbonate secretion in rat duodenum. AJP Gastrointest Liver Physiol 2012; 303:G810–G816.
42. Drucker DJ. Minireview: the glucagon-like peptides. Endocrinology 2001; 142:521–527. [PubMed: 11159819]
43. Engelstoft MS, Egerod KL, Holst B, Schwartz TW. A gut feeling for obesity: 7TM sensors on enteroendocrine cells. Cell Metab 2008; 8:447–449. [PubMed: 19041758]
44. Lu W, Yang Q, Yang L, Lee D. Chylomicron formation and secretion is required for lipid-stimulated release of incretins GLP-1 and GIP. Lipids 2012; 47:571–580. [PubMed: 22297815]
45. Christensen LW, Kuhre RE, Janus C, et al. Vascular, but not luminal, activation of FFAR1 (GPR40) stimulates GLP-1 secretion from isolated perfused rat small intestine. Physiol Rep 2015; 3:pii: e12551. [PubMed: 26381015]
46■. Psichas A, Larraufie PF, Goldspink DA, et al. Chylomicrons stimulate incretin secretion in mouse and human cells. Diabetologia 2017; 60: 2475–2485. [PubMed: 28866808] This study provides evidence that GLP-1 secretion may occur in response to the lipolysis of chylomicrons by lipoprotein lipase in vitro.
47. Rocca AS, Brubaker PL. Role of the vagus nerve in mediating proximal nutrient- induced glucagon-like peptide-1 secretion. Endocrinology 1999; 140:1687–1694. [PubMed: 10098504]
48. Guerville M, Boudry G. Gastrointestinal and hepatic mechanisms limiting entry and dissemination of lipopolysaccharide into the systemic circulation. Am J Physiol Gastrointest Liver Physiol 2016; 311:G1–G15. [PubMed: 27151941]
49. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 2007; 56:1761–1772. [PubMed: 17456850]
50. Erridge C, Attina T, Spickett CM, Webb DJ. A high-fat meal induces low-grade endotoxemia: evidence of a novel mechanism of postprandial inflammation. Am J Clin Nutr 2007; 86:1286–1292. [PubMed: 17991637]
51. Ghoshal S, Witta J, Zhong J, et al. Chylomicrons promote intestinal absorption of lipopolysaccharides. J Lipid Res 2009; 50:90–97. [PubMed: 18815435]
52. Maruta K, Akiba Y, Kaji I, Kaunitz JD. Rapid LPS transport during long-chain fatty acid absorption in rat small intestine. Gastroenterology 2017; 152:S201.
53. Akiba Y, Kaji I, Maruta K, Kaunitz JD. GLP-2 acutely ameliorates LPS-related intestinal permeability in rats. Gastroenterology 2017; 152:S506.

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KEY POINTS

- Receptors expressed on enteroendocrine cells sense the luminal environment, releasing hormones and other bioactive substances.
- Bacterial metabolites such as short chain fatty acids are sensed by their cognate GPCR FFA2 and FFA3.
- Bile acids and bile acid metabolites are sensed by the GPCR TGR5, which when expressed on enteroendocrine L cells, releases the insulinotropic hormone GLP-1.
- Bacterially derived LPS is transported through the intestinal mucosa by transcellular and paracellular pathways.
- Study of intestinal chemosensory mechanisms will provide key data regarding the mechanism by which the gut microbiota interacts with the host.