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Duodenal chemosensory system: enterocytes, enteroendocrine cells, and tuft cells

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Abstract

Purpose of Review: The gut barrier serves as the primary interface between the environment and host in terms of surface area and complexity. 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 subepithelial space. In this review, we have summarized recent advances in the understanding of the luminal chemosensory system in the gastroduodenal epithelium consisting of enterocytes, enteroendocrine, and tuft cells, with particular emphasis on how chemosensing affects mucosal protective responses and the metabolic syndrome.

Recent Findings: Recent single cell RNA sequencing provides detailed cell type-specific expression of chemosensory receptors and other bioactive molecules as well cell lineages; some are similar to lingual taste cells whereas some are gut specific. Gut luminal chemosensing is not only 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 will discuss the chemosensory mechanisms of the proximal intestine, in particular to gastric acid, with a focus on the cell types and receptors involved in chemosensing, with emphasis on the rare chemosensory cells termed tuft cells. We will also discuss the chemosensory functions of intestinal ectoenzymes and bacterial components (e.g., lipopolysaccharide (LPS)) as well as how they affect mucosal function through altering the gut-hormonal-neural axis.

Summary: Recent updates in luminal chemosensing by different chemosensory cells have provided new possibilities for identifying novel molecular targets for the treatment of mucosal injury, metabolic disorders, and abnormal visceral sensation.

Keywords

Gut Chemosensing; Lipopolysaccharide; G protein-coupled receptors; Gut hormones; Glucagon-like peptides; Ecto-enzymes; Solute carrier family; Enteroendocrine cells; Tuft cells

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Conflicts of interest
None

Introduction

The duodenal mucosa is exposed to a mixture of undigested and digested food, secreted gastric acid and bile acids, bacterial components and metabolites, and damage-associated molecular patterns (DAMPs). 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 (GI) tract has accelerated due to the de-orphanization and characterization of nutrient-sensing G protein-coupled receptors (GPCRs). These bioactive compounds also include bacterial and cellular metabolites, which are recognized by recently discovered specific receptors, termed metabolite sensing [2]. Gut luminal chemosensing is implicated not only in the regulation of gut function, but also in the systemic regulation of metabolism, energy balance, and food intake [1].

Gut physiological functions such as secretion, digestion, absorption, and motility are regulated by these luminal substances, in addition to neural regulation by the central nervous system (CNS) via vagal nerves activated during the cephalic phase of food intake. The first discovery of gut hormone release in response to a luminal substance was secretin, released in response to luminal acid (H^+) [3]. To date, ~20 gut hormones, principally localized in enteroendocrine cells (EECs) or myenteric neurons of the submucosal and myenteric plexus in the GI tract have been identified. Extensive studies have clarified the contributions of these gut hormones to 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 and its effector receptor activation of subepithelial afferent nerves is not well understood.

In this review, we will summarize recent reports addressing luminal chemosensing in the duodenal mucosa focusing on mucosal protective responses and the contribution of chemosensory cell types to luminal contents.

Components of chemosensory system in the GI mucosa

Luminal bioactive molecules of endogenous and exogenous origin are primarily exposed to the luminal surface of the epithelial cells, including villous cells, EECs, and tuft cells (TCs). Recent advances have revealed the identification of detailed molecular profiles of EECs and TCs, including their cell lineage, specific markers, and functions. Most of the nutrient and metabolite receptors are GPCRs, located on the apical membranes and/or basolateral membranes of villous cells, EECs or TCs. Furthermore, luminal compounds are absorbed through apical and basolateral transporters of solute carrier (SLC) families. Chemosensory receptor GPCRs expressed on subepithelial afferent nerves are directly activated by luminal compounds transported across the epithelium via solute transporters (SLCs). Sensory nerve GPCRs are also activated secondarily by released stored or newly synthesized mediators and gut hormones present in EECs and probably in TCs. Activation of the afferent nerves conducts luminal information to internal neural circuits via the local neural network of myenteric neurons in order to exert local physiological responses, such as secretion and motility, to the CNS via vagal afferents that influence food intake and vagal reflexes, and to

remote organs that regulate hormonal function that affect metabolic and energy regulation. Recent advances also reveal the close or direct anatomical and functional interactions of EECs [4] and TCs [5] with subepithelial nerve fibers. These patterns were highlighted in our previous review article [1].

Acid chemosensory mechanisms

Villous cells are absorptive epithelial cells that possess brush border ecto-enzymes whose catalytic activities are present outside of the cells. Ecto-enzymes digest micronutrients, disaccharides, and peptides into absorbable nutrients such as monosaccharides, dipeptides, and amino acids. The ecto-enzymes related to luminal chemosensing include carbonic anhydrase (CA) for acid sensing [6,7], intestinal alkaline phosphatase (IAP) for ATP sensing [8,9] and adenosine (ADO) deaminase (ADA) for ADO sensing [10]. Small intestinal brush border ecto-enzymes also contain peptidases. Dipeptidyl peptidase 4 (DPP4) rapidly degrades gut hormones including glucagon-like peptide-1 (GLP-1), GLP-2, gastric inhibitory polypeptide (glucose-dependent insulinotropic polypeptide, GIP), vasoactive intestinal polypeptide (VIP), and pituitary adenylate cyclase-activating polypeptide (PACAP) [11,12]. Interestingly, DPP4 (CD26) is an ADA-binding protein located also on the cell surface of T cells [13], suggesting the costimulatory regulation of ADO and DPP4 substrate peptides on immune cells. Angiotensin-converting enzyme (ACE), that converts angiotensin-I to angiotensin-II, and ACE2, that converts angiotensin-II (vasoconstrictor) to angiotensin(1–7) (vasodilator), are also highly expressed on duodenal brush border membranes [14–16]. Despite their high expression levels, the physiological functions of these hormone peptidases with regard to GI function are unknown, since the corresponding substrate hormones may not be found or released into the lumen. Interestingly, these ecto-enzymes serve as receptors for pathogenic coronaviruses; ACE2 for the viruses causing the severe adult respiratory syndrome (SARS) [17] and SARS-CoV-2 [18], and DPP4 for middle east respiratory syndrome (MERS) [19].

Luminal acid sensing in the duodenum is important to protect the mucosa from acid-induced injury. Duodenal acid sensing mechanisms consists of a multistep pathways 1) H^+ is converted to CO_2, in the presence of basally secreted HCO_3^-, by ecto-enzyme membrane-bound CA activity [7], 2) CO_2 is absorbed by villous cells, followed by conversion to H^+ by cytosolic CA [6], 3) H^+ is extruded via the basolateral Na^+/H^+ exchanger 1 (NHE1; SLC9A1), which then activates the H^+ sensor, termed transient receptor potential (TRP) vanilloid 1 (TRPV1) expressed on capsaicin-sensitive afferent nerves, 4) capsaicin-sensitive afferent nerves release calcitonin-gene related peptide (CGRP) and nitric oxide (NO) resulting in a hyperemic response [20], 5) HCO_3^- is loaded into the enterocytes via the basolateral Na^+:HCO_3^- cotransporter 1 (NBC1; SLC4A4) [21], and, finally, 6) HCO_3^- is secreted via the cystic fibrosis transmembrane conductance regulator (CFTR) [22,23]. This process facilitates further CO_2 absorption via the Jacob-Stewart cycle [7]. The net effect is that duodenal mucosal sensing of luminal acidity evokes a series of steps, including activation of CA, ion transporters, and neuronal acid sensor TRPV1, that serves to protect the mucosa from damage [1].

Other ecto-enzymes implicated in luminal chemosensing include the purine metabolizing enzymes IAP and ADA. IAP is a glycosylphosphatidylinositol (GPI) anchored ecto-enzyme highly expressed in the brush border membrane of duodenal epithelial cells [8]. Since the optimal pH of IAP is 8 – 9 and IAP activity is closely correlated with the secretory rate of HCO_3^- [8], IAP may act as a surface pH sensor in the duodenum, as part of a system that preserves extracellular pH homeostasis. At neutral luminal pH, extracellular ATP, non-lytically released from the epithelial cells, is rapidly degraded to ADO by IAP, which is further degraded by ADA to inosine. Once the surface pH is lowered by gastric acid, surface ATP concentrations increase due to reduced IAP activity at acidic pH, with a consequent decrease in ATP metabolism. Increased surface ATP concentrations activate purinergic P2Y receptors expressed on the apical membrane of epithelial cells, stimulating HCO_3^- secretion. Increased surface [HCO_3^-] increases the surface pH, increasing IAP activity, which degrades surface ATP, terminating ATP-P2Y signaling [9]. Luminal ADO additionally stimulates HCO_3^- secretion via A2B receptors (A2BR), followed by ADO degradation by ADA and by ADO absorption via apical nucleotide transporters SLC28 and SLC29 [10]. These studies suggest that IAP acts as a pH sensor that modifies surface ATP concentrations, as part of a negative feedback loop. This ecto-purinergic signaling encompasses villous cell purine sensing by ecto-enzymes (IAP and ADA) and apical GPCRs (P2Y and A2BR) to regulate the surface microclimate pH of the duodenum. A similar mechanism of purinergic extracellular pH regulation has been implicated in the mechanism of bone resorption by osteoclasts [24].

Enteroendocrine cells (EECs), nutrient GPCRs, gut hormone release and the gut-neural axis

EECs comprise 4.3% of all intestinal epithelial cells [25]. Duodenal EECs contain a broad spectrum of peptides/hormones/amines [26], including the traditionally named serotonin (5-hydroxytryptamine, 5-HT)-containing enterochromaffin (EC) cells, cholecystokinin (CCK)-containing I cells, secretin-containing S cells, somatostatin-containing D cells, GIP-containing K cells, GLP-1/GLP-2-containing L cells, and neurotensin-containing N cells. Some populations of EECs co-express multiple hormones due to a common cell lineage [27]. EECs also express a variety of nutrient-sensing GPCRs [28,29], suggesting that the duodenal EECs sense different nutrients and other bioactive molecules via cognate GPCRs, followed by selective release of gut hormones in order to regulate the local neural and systemic metabolic responses.

Fine ultrastructural imaging using 3D electron microscopy reveal that EECs are closely connected with neurons by neuropods [4]. Monosynaptic rabies virus tracing from lumen to subepithelial nerves [30] indicates that the epithelium monitors the luminal environment by subepithelial sensory neural pathways. TCs are also closely apposed to subepithelial nerves [5]. These findings suggest that epithelial chemosensory systems constitute a local gut-neural axis, consisting of epithelial cells, EECs, and TCs connecting to subepithelial afferent nerves, which may relay luminal information to the local neural circuitry and on to the CNS.

EC cells, containing >90% of body's entire content of serotonin (5-HT) [31], are proposed polymodal gut chemosensors responsive to luminal irritants and bacterial metabolites [32].

5-HT, released from EC cells, induces physiological and pathophysiological responses in local and systemic organs, including gastrointestinal secretion and motility, emesis (nausea and vomiting), and visceral hypersensitivity [33–35]. Studies using model endocrine tumor cell lines and ex vivo whole tissue preparations [36–41] have demonstrated that numerous stimuli release 5-HT from EC cells, whereas the exact mechanisms of 5-HT release and communication with the nervous system have not been fully elucidated. Labelled EC cells in intestinal organoids, with released 5-HT monitored using a 5-HT_3 receptor-expressing single cell biosensor, demonstrate that TRP ankyrin 1 (TRPA1) is an irritant receptor, olfactory receptor 558 (Olfr558) is a microbial metabolite sensor, and 2A adrenoceptor (Adra2A)-TRP canonical 4 (TRPC4) channel is a catecholamine sensor, all interacting with 5-HT_3 receptor-positive afferent nerve fibers in order to conduct luminal chemical information to the nervous system [32].

We have observed that the serosally-applied selective 5-HT_3R agonist SR57227 increases electrogenic anion secretion in the duodenum and proximal colon of rat and mouse; the effects are ~50% inhibited by a 5-HT_4R antagonist and ~50% inhibited by a VIP/PACAP receptor 1 (VPAC1) antagonist [42]. 5-HT_3R is immunolocalized to EC cells and myenteric neurons [43], and 5-HT_3R is colocalized with VIP in subepithelial nerves [42]. 5-HT_4R is present in the basolateral membranes of epithelial cells [44,45]. These results suggest that serosal 5-HT_3R agonists stimulate both VIP-positive nerve fibers and EC cells to release VIP and 5-HT, respectively, followed by activation of epithelial VPAC1 and 5-HT_4R. Both VPAC1 and 5-HT_4R activation increase intracellular cAMP, that, in turn, activates CFTR, with resultant electrogenic Cl^-/HCO_3^- secretion. Therefore, luminal irritants, odors, bitter tastants, bacterial metabolites, pathogenic bacteria and viruses, and chemotherapeutic agents all release 5-HT from EC cells and may share this neural-epithelial circuit to induce, if excessive, massive anion secretion, causing diarrhea. Thus, 5-HT_3R antagonists, 5-HT_4R antagonists, and VPAC1 antagonists may prove useful to treat 5-HT-related diarrheal diseases [46,47].

TCs: neural and immune phenotypes

TCs, first described in rat trachea and mouse glandular stomach in 1956 [48,49], are a rare, but distinct, lineage of epithelial cells, morphologically termed tuft, brush, caveolated, multivesicular, or fibrillovesicular cells [48]. Although cells that morphologically resemble lingual taste cells have been recognized in the GI tract for decades [50], EECs and TCs had heretofore not been functionally distinguishable. Solitary cells found at the surface epithelium of the intestinal villi or in the glands, disseminated throughout the GI tract, express taste signaling proteins including taste receptor 1 (Tas1r), taste receptor 2 (Tas2r), G-protein α-gustducin, α-transducin, phospholipase Cβ2 (PLCβ2), and TRP menthol 5 (TRPM5) [51–54]. Therefore, intestinal TCs are considered chemosensory cells, resembling type II taste cells in the taste buds, which sense sweet, *umami*, and bitter tastes [55]. Doublecortin and calcium/calmodulin-dependent protein kinase-like 1 (DCAMKL1/DCLK1) has been used as a specific TC marker protein [56]. The number of DCLK1-positive TCs along the small intestine and colon in mice is greatest in the upper small intestine and lower in the ileum and colon [5], supporting the chemosensory functions of TCs present in the duodenum.

TCs are present in the digestive system including the salivary glands, stomach, small intestine, cecum, colon, gall bladder, bile duct, and pancreatic ducts as well as the respiratory system, urethra and thymus. TCs require the atonal homologue 1 (ATOH1)/mouse atonal homologue 1 (MATH1) transcription factor for their differentiation, but not neurogenin 3 (Neurog3), SRY-Box containing gene 9 (SOX9), growth factor-independent 1 (GFI1), or SAM pointed domain containing ets transcription factor (SPDEF), all of which are essential for EEC, Paneth cell, and goblet cell differentiation [57], suggesting that TCs are produced by distinct lineages derived from other cells. The discovery and expression of the taste cell specific transcriptional factor Skn-1a/Pou2f3 [58] suggests a common taste cell lineage for lingual taste buds and TCs present in the GI tract and airway. Skn-1a/Pou2f3 determines the differentiation of sweet, *umami*, and bitter taste receptor cells [58]. Skn1a/Pou2f3 KO mice lack TRPM5-positive brush cells in the trachea and lack TRPM5-, DCLK1-positive TCs in the stomach, small intestine and colon [59], confirming that Skn1a/Pou2f3 is a master and common regulator of TRPM5-positive chemosensory cells, type II taste cells, and TCs.

Gene expression of TRPM5-expressing cells in murine intestine using Trpm5-GFP mice identify the detailed profiles of TCs that express not only taste receptor signaling genes (α-gustducin, PLC β2/PLCγ2 and Trpm5) and known TC markers (advillin, cytokeratin 18 (CK18), Dclk1), but also neuroendocrine pathway genes (presynaptic proteins, proteins involved in exocytosis of synaptic vesicles, secretin, tachykinin 1, and low expression of chromogranin A and CCK and GIP), and inflammatory pathway genes, cyclooxygenase (COX)-1 (Ptgs1), COX-2 (Ptgs2), phospholipase A2 group IVA (PLA2g4a), leukotriene C4 synthase (Ltc4s), arachidonate 5-lipoxygenase (Alox5), interleukin (IL)-17e (also known as IL-25) [60]. Furthermore, Trpm5-expressing cells specifically express succinate receptor 1 (Sucnr1; GPR91). These observations will likely spur further study of the links between TCs and the Th-2 immune system.

Another interesting overlap relates to cholinergic markers in TCs. The acetylcholine (ACh) synthesizing enzyme choline acetyltransferase (ChAT) is expressed not only in mouse central and peripheral cholinergic neurons, but also in epithelial cells in lung and intestine [61]. Further study identified ChAT-containng cells as TCs along the small intestine and colon. These cells co-express CK18, TRPM5, COX-1 and COX-2, but essential cholinergic proteins, such as the high-affinity choline transporter (ChT1) for extracellular choline uptake and the vesicular acetylcholine transporter (VAChT) for concentrating ACh into the vesicles, are not found in small intestinal TCs [62]. These results suggest that epithelial cholinergic cells are TCs, which may use an alternate choline uptake pathway (e.g. organic cation transporters) and ACh storing system rather than canonical neuronal cholinergic mechanisms. The study also demonstrates that ChAT-containng cells are not colocalized with EEC markers and hormones (chromogranin A, somatostatin, substance P, 5-HT, GIP, neurotensin, PYY, CCK, secretin and β-endorphin), suggesting that ChAT-positive TCs are a distinct population from EECs.

Functional evidence of TC-derived ACh release related to luminal chemosensing has not been studied in the small intestine. ACh release from TCs in the olfactory epithelium (TRPM5-positive microvillous cells) in response to luminal ATP and odor mixtures [63],

and from TCs in the airway epithelium (ChAT-positive brush cells) in response to luminal bitter tastants [64] have been reported. Non-neuronal epithelial synthesis and release of ACh in response to luminal short-chain fatty acid propionate has been reported in the rat distal colon [65,66]. ACh release from TCs in the small intestine is implicated to the stem cell homeostasis via epithelial cholinergic niche [67]. Functional roles of small intestinal TC-releasing ACh is awaited regarding the luminal chemosensing.

Sorting of TRPM5-containing cells demonstrate that these cells, representing 0.6% of total epithelial cells, specifically express not only the TC markers DCLK1, GNAT3, PLC2 and TRPM5, but also SUCNR1 and IL-25 [68]. TCs initiate type 2 immunity in response to helminth parasites, in part, by secreting IL-25 [69]. A type 2 immune response with proliferation of TCs and goblet cells along with increased expression of IL-13 in the jejunum of wild type but not SUCNR1 knockout mice was also observed when succinate (100 mM) was added to the drinking solution [68], suggesting that luminal succinate derived from the diet, microbiota, or parasitic worms that produce succinate can trigger type 2 immunity.

The expression of TRPM5 and involvement of TRPM5 in the release of gut hormones and mediators are not limited to TCs but also occur in EECs. In STC-1 cells, a model cell line of gut endocrine cells, linoleic acid increases CCK release via a FFA4, PLC2, TRPM5 and voltage-gated calcium channel (VGCC)-dependent pathway, suggesting that TRPM5 is also involved in gut hormone release from EECs [70]. Furthermore, studies examining insulin release from isolated pancreatic islet cells from wild type, TRPM4 KO, and TRPM5 KO mice indicates that GLP-1 stimulates insulin secretion by PKC-dependent activation of TRPM4 and TRPM5 [71].

In the small intestine of mice, up to 80% of DLCK1-positive TCs contain 5-HT in their apical regions, more so for those located in the upper small intestine, but lack expression of tryptophan hydroxylase (TPH), the rate-limiting enzyme responsible for 5-HT synthesis [72]. The findings suggest that TCs store, possibly via the serotonin reuptake transporter (SERT), but may not be able to synthesize 5-HT.

TCs may be classified, according to RNA expression profiles, into two subtypes, neural or tuft-1 and immune/inflammatory or tuft-2 [25]. DCLK1 is a universal marker for TCs whereas other markers are heterogeneously expressed such as Hopx, p-EGFR, Ac Tub, Cox1, Cox2, Sox9 and Lgr5 [60], [73].

Increased TC density was reported in colonic biopsies of patients with diarrhea-predominant irritable bowel syndrome (IBS) compared with constipation-predominant IBS (IBS-C) and healthy controls [74]. It is unclear whether the TC density of 0.3% of total cells in IBS-D compared with 0.2% in control patients is clinically significant or even related to IBS-D pathogenesis, especially since the abundance of TCs in the small intestine, albeit in mice, is much higher, ~2.3% of total epithelial cells and increases five-fold with succinate feeding [25,68,75].

Regulation of luminal lipopolysaccharide (LPS) and transport

LPS, an endotoxin present in the outer coat of Gram-negative bacteria, has been implicated in acute and chronic inflammation. IAP detoxifies LPS by dephosphorylating its toxic lipid A moiety [76], thus preventing activation of its pro-inflammatory receptor, Toll-like receptor 4 (TLR4) [77]. Since 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 [78]. Furthermore, IAP deficiency is associated with inflammation due to increased LPS toxicity in the human intestine [79] and in the intestines of vertebrate models in which IAP levels are decreased [78]. *In vivo*, however, the localization of IAP and LPS is mismatched - IAP is expressed predominantly in the upper small intestine, duodenum, and jejunum [8], whereas LPS, which is predominantly derived from Gram negative bacteria, is at highest concentrations in the ileum and colon [80]. It is conceivable that IAP, cleaved from the brush border membrane by phosphatidylinositol-specific phospholipase C (PI-PLC), may enter the lumen and be transported to the ileum and colon where it may detoxify luminal LPS. Excessive LPS in the upper small intestine, that exceeds the capacity of IAP-mediated detoxification, may be transported through the mucosa, activating TLR4 expressed on epithelial and inflammatory cells that are implicated on the pathogenesis of the syndrome termed “metabolic endotoxemia” (the metabolic syndrome accompanied by chronic modest elevations of serum LPS) and inflammation [81]. Oral administration of bovine IAP improves the metabolic syndrome induced by a high-fat diet [82], impairs the development of experimental colitis [83], and reduces alcoholic hepatosteatosis [84], suggesting that IAP detoxification reduces the pro-inflammatory effects of LPS.

Circulating LPS increases the paracellular permeability of the gut mucosal barrier, associated with increased LPS translocation into the circulation, augmenting endotoxemia with consequent systemic inflammation [85]. LPS aggravates low-grade inflammation [85], high-fat meals acutely increase circulating LPS levels in human healthy volunteers, [86] and LPS appears in chylomicron remnants in mice [87], suggesting that luminal LPS physiologically crosses the gut barrier during fat absorption. We have demonstrated 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* [80]. Exogenous GLP-2 also reduces LPS transport into the portal vein via pathways involving VIP and NO, suggesting that GLP-2 treatment may be a novel therapy for the prevention and treatment of metabolic endotoxemia [80]. We have also observed that acute administration of GLP-2 reduces LPS-induced increased intestinal paracellular permeability by a mechanism that is not likely related to the known hypertrophic and hyperproliferative effects of chronic GLP-2 administration [88]. Therefore, exogenous GLP-2 treatment may be of value in the prevention of systemic inflammation associated with endotoxemia due to a “leaky gut” [89].

Conclusions

The gut epithelial chemosensory system senses luminal bioactive molecules, transmitting this information to subepithelial afferent nerves, which in turn, activate local effector

systems that regulate secretion, digestion, absorption, motility, and mucosal defense. Recent studies incorporating single-cell profiling have provided detailed descriptions of the chemosensory mechanisms present in the specialized epithelial cells of the small intestinal mucosa and have illuminated the signaling cascades induced by chemosensing combined with released mediators, their receptors on neural circuitry and epithelial cells, and local and remote effects of released hormones. Recent discoveries of the diverse mechanisms by which luminal components are sensed by the mucosa have identified novel molecular targets for the treatment of mucosal injury, metabolic disorders, and abnormal visceral sensation.

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Key points

- The duodenal mucosa senses luminal molecules and transmits this information, via neural and hormonal pathways, to actuate local and systemic physiological responses.
- Duodenal chemosensory system consists of ecto-enzymes, receptors, transporters, enteroendocrine cells, and tuft cells, the activation of which releases gut hormones and activates subepithelial afferent nerves.
- Understanding the mechanisms and pathways involved in luminal chemosensing may open the door for the discovery of novel therapeutic targets and agents to prevent mucosal injury, promote mucosal healing, and treat IBS as well as the metabolic syndrome.