**Title**
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**Journal**
Current Opinion in Gastroenterology, 33(6)

**ISSN**
0267-1379

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**Publication Date**
2017-11-01

**DOI**
10.1097/mog.0000000000000396

Peer reviewed

HHS Public Access

Author manuscript

*Curr Opin Gastroenterol*. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

*Curr Opin Gastroenterol*. 2017 November ; 33(6): 439–445. doi:10.1097/MOG.0000000000000396.

# Luminal chemosensing in the gastroduodenal mucosa

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## Abstract

**Purpose of review—**We report recently published knowledge regarding gut chemosensory mechanisms focusing on nutrient-sensing G protein-coupled receptors (GPCRs) expressed on gut enteroendocrine cells (EECs), tuft cells, and in afferent nerves in the gastroduodenal mucosa and submucosa.

**Recent findings—**Gene profiling of EECs and tuft cells have revealed expression of a variety of nutrient-sensing GPCRs. The density of EEC and tuft cells is altered by luminal environmental changes that may occur following bypass surgery or in the presence of mucosal inflammation. Some EECs and tuft cells are directly linked to sensory nerves in the subepithelial space. Vagal afferent neurons that innervate the intestinal villi express nutrient receptors, contributing to the regulation of duodenal anion secretion in response to luminal nutrients. Nutrients are also absorbed via specific epithelial transporters.

**Summary—**Gastric and duodenal epithelial cells are continually exposed to submolar concentrations of nutrients that activate GPCRs expressed on EECs, tuft cells, and submucosal afferent nerves and are also absorbed through specific transporters, regulating epithelial cell proliferation, gastrointestinal (GI) physiological function, and metabolism. The chemical coding and distribution of EECs and tuft cells are keys to the development of GPCR-targeted therapies.

### Keywords

Enteroendocrine cell; tuft cell; afferent nerve; nutrient receptors; gastrointestinal mucosa

## Introduction

Gastric and duodenal epithelial cells are continually exposed to mM ranges of nutrients, gastric acid, bacterial metabolites, and bile acids that activate distinct G protein-coupled receptors (GPCRs), including sweet taste/umami receptors (taste receptor type 1, T1R1-3), members of the bitter receptor family (T2R), the bile acid receptor (GPBA), medium- and long-chain fatty acid receptors (FFA1, FFA4, GPR84, GPR119), short-chain fatty acid

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Conflicts: None

receptors (FFA2, FFA3), metabolic L-glutamate receptors (mGluRs), the lysophosphatidic acid receptor (LPA5), and the calcium sensing receptor (CaSR). Consistent with human taste concentration thresholds for sweet, umami, bitter, salty, and sour tastes (10 mM sucrose, 2 mM L-glutamate, 0.1 mM propylthiouracil, 17 mM Na+, and 2 mM acetic acid, respectively), most of those GPCRs are activated by ingested nutrients in mM ranges. Mucosal enteroendocrine cells (EECs) and tuft cells are considered to be gastrointestinal (GI) chemosensory cells that monitor luminal nutrients with the aforementioned GPCRs as well as nutrients transported into the submucosa, releasing distinct bioactive molecules in response to GPCR activation. EECs, consisting of ~1% of the epithelial cell population, are essential for chemosensory regulation of physiological digestive functions and systemic metabolism through paracrine, neurocrine, and endocrine pathways. Another secretory epithelial lineage, tuft cells, is also an uncommon but important epithelial cell population also essential for foregut chemosensing. Mutation of the transcription factor neurogenin-3 prevents EEC differentiation with resulting malnutrition in human and mice models [1;2]. Duodenal EEC density is significantly decreased in irritable bowel syndrome (IBS) or in functional dyspepsia (FD) patients [3;4], suggesting the importance of EEC-neuronal signals in GI physiological and afferent functions. Extrinsic afferent nerves that innervate the GI mucosa receive transduction signals from EECs and tuft cells through synapse-like structures and also directly monitor submucosal nutrients via nutrient-sensing GPCRs after absorption through the mucosa (Figure 1).

### Chemosensory cells in the gastroduodenal mucosa

## EECs

EECs release important gut hormones such as 5-hydroxytryptamine (5-HT), gastric inhibitory peptide (GIP), cholecystokinin (CCK), glucagon-like peptides (GLP)-1, and GLP-2 into the portal vein or lymph [5–9]. EEC density is highest in the proximal duodenum, in particular 5-HT-producing enterochromaffin (EC) cell in the human intestine [10]. In 1962, the luminal release of 5-HT from rat duodenum in response to luminal acid was described [11], followed by isolated EC cell responses to a variety of food ingredients associated with nutrient receptor activations [12–14]. Similarly, the observation that luminal nutrients stimulate the release of GIP, CCK, GLP-1 and 2 [5–9] supported the hypothesis that EECs are intestinal ‘taste cells’ or ‘chemosensors’. Recent gene expression profiling studies suggest that EEC characteristics are based on a combination of GPCRs that vary among GI segments [14*,15,16]. In contrast to the classical EEC concept, some gut peptides are present in EECs in unexpected combinations; the mRNA coding for CCK, secretin, GIP, GLP-1, PYY, and neurotensin (NT), but not somatostatin, are co-expressed in a novel grouping of EECs [17]. Indeed, double-immunostaining studies confirm that GIP and GLP-1 are frequently co-expressed in rat duodenal EECs [18], 5-HT and CCK are often co-expressed in mouse duodenal EECs [19]. A subset of EECs co-express xenin-25, a homologue of NT, along with GIP but not 5-HT in canine duodenum [20], whereas xenin-25 is present in a subset of 5-HT/CCK- and GLP-2-expressing EECs rather than in GIP-producing EEC of rat duodenum [21*]. These observations suggest that multiple hormones can be released simultaneously, activating distinct local and metabolic pathways in response to luminal nutrient ligands.

Although isolated cell studies confirmed the predominant receptor profiles in each intestinal segment, in vitro experimental systems are not able to preserve physiological cell polarity. Since the immunoreactivity of many nutrient GPCRs is often detected in the cytosol, it is not always apparent which side (apical or basolateral) of the epithelial cells express nutrient GPCRs. Christensen et al. demonstrated that GLP-1 secretion from an isolated segment representing the proximal third of the small intestine (duodenum and proximal jejunum) was stimulated by intravascularly administered FFA1 synthetic agonists rather than by luminal agonists [22]. Although the duodenal luminal perfusion of FFA2 agonists releases 5-HT into the portal vein [23*], isolated duodenal EC cells are not directly activated by FFA2 ligands [14]. Furthermore, the glucose transporters GLUT2 and SGLT1 are essential to the activation of GIP and GLP-1 release [24;25]. These findings suggest that nutrient absorption prior to nutrient GPCR activation is an alternative pathway for the activation of EECs.

Gastric EECs are localized to the lower half of gastric glands, with the acid-producing oxyntic mucosa and acid-sensing antrum having different EEC populations [26]. The gastric corpus has a large population of ‘closed’ type EECs expressing the hunger-stimulating hormone ghrelin. Ghrelin-producing EEC lacks direct access to the lumen, but expresses a variety of nutrient GPCRs such as T1R3, FFA2, FFA4, GPR84, and CaSR [27;28]. Postprandially, the plasma may contain sufficient concentrations of all of these GPCR ligands such as amino acids, acetate, and free fatty acids to inhibit ghrelin release [28]. Gastrin, which stimulates gastric acid secretion through histamine release, is produced by open-type EEC localized exclusively in the antrum. Gastrin-producing cells express the GPCRs LPA5, GPRC6A, and CaSR, which are activated by amino acids, pH elevation, and/or extracellular Ca++ [29;30]. The same GPCRs are expressed by somatostatin-producing EEC [29], and FFA2 is expressed by 5-HT-producing EEC [31]. Both types of EEC are distributed in corpus and antrum, whereas the association of nutrient GPCR activation to somatostatin or 5-HT release is unknown.

## Tuft Cells

Tuft cells (also termed as brush, caveolated, or fibrillovesicular cell) are also considered to be intestinal taste cell due to their expression of T1Rs, the Ca++-gated monovalent cation channel transient receptor potential subfamily M (TRPM)5, and gustducin, all molecules important for taste transduction. Differentiation into tuft cells depends on the transcription factor atonal homolog (ATOH)1, similar to other secretory cells (EEC, goblet, and Paneth), but not requiring neurogenin 3, which is essential for EEC differentiation, indicating that tuft cells are distinct from EECs [32]. Electron microscopy identified tuft cells morphologically by long apical microvilli, narrow rootlets, and well-developed tublovesicular structures in the cytoplasm. Tuft cells are present throughout GI tract, including in salivary and bile ducts [33]; they express many bioactive molecules, such as nitric oxide in rat stomach [34], ACh in mouse stomach [35], guanylin in human duodenum, but not in rat duodenum [36*], opioids, uroguanylin, and prostaglandins in mouse duodenum [37;38]. Since tuft cells lack chromogranin-positive granules, they may synthesize transmitters de novo, releasing them predominantly into the lumen. Doublecortin-like kinase 1 protein (DCLK1) and cytokeratin (CK)-18 are well characterized brush cell markers, identified in the rodent fundus, antrum, and duodenum. Duodenal tuft cells express gustducin, T1R1, and T1R3 in mice [39],

suggesting the involvement in sweet receptor-dependent glucose transporter upregulation [40].

In the upper half of gastric glands and a few proximal corpus glands beneath the 'limiting ridge' in rodent stomach exists a unique population of tuft cells, which express gustducin, T1R3, FFA2, FFA3, and FFA4 [27;41;42]. Gastric tuft cells have an apical membrane projection that reaches the lumen, consistent with their proposed chemosensory functions. Transcription levels of the bitter taste receptor T2R108 and gustducin are relatively higher in the mouse stomach than in other intestinal regions, downregulated by 18-hour-fasting and recovered by only 4-hour-refeeding [43]. Although a T2R-expressing gastric cell type has not been identified, these dynamic changes of chemosensor expression support the nutrient sensing function of specialized cells within the gastric mucosa.

## EEC adaptation following bariatric surgery

Bariatric surgery noticeably improves severe obesity and type 2 diabetes with a low risk of relapse [44;45]. Fasting-stimulated increases in the plasma levels of ghrelin are abolished by vertical sleeve gastrectomy in a rodent model and are unaffected in the Roux-en-Y gastric bypass (RYGB) model [46]. Interestingly, ghrelin-deficient mice comparably decrease food intake and body weight in both models, suggesting that bariatric surgery-induced weight loss is independent of the ghrelin-stimulated hunger signal [46]. Bypassing the duodenum without changing gastric volume increases the unique population of EECs that co-produce the incretin hormones GIP and GLP-1, improving pancreatic function in diabetic model rats [18]. The rat RYGB model that has an 80% decrease in stomach volume increases mucosal growth factor expression and crypt cell proliferation associated with circulating GLP-2 increase two weeks following surgery [47], consequently increasing EECs expressing GLP-1, CCK, NT, or 5-HT, associated with mucosal hyperplasia in the distal small intestine after 10–11 months [48]. In human obese patients with and without type 2 diabetes, the density of GIP-, GLP-1- or CCK-producing EECs are increased in the jejunum by RYGB [49]. An increase in postprandial GLP-1 caused by intestinal adaptation is likely to contribute towards improving glucose control and countering obesity. Although GIP stimulates insulin secretion, high-fat diet-induced excess GIP secretion is associated with insulin intolerance, rescued by GIP receptor deficiency [50]. Selective antagonism of the GIP pathway may be a therapeutic target for metabolic disorders.

## Tuft cell population changes in pathological states

Tuft cell density appears to be a marker of gastrointestinal mucosal pathology. Hyperproliferation of tuft cells is frequently present in mouse and human intestinal adenomata, and in mouse stomach in which inflammation, hyperplasia, and metaplasia is present. Tuft cell hyperplasia is also implicated in GI tumorigenesis linking of excess prostanoid production due to the cyclooxygenase (COX)-2 expression in tuft cells [32;51]. Chemically and genetically induced fundic metaplasia markedly increase the density of DCLK-positive tuft cells in mouse models, and restore the tuft cell population coincident with mucosal restitution [52]. Tuft cells expressing interleukin-25 are increased by small intestinal worm infection [53], further implicating a new function of tuft cells in mucosal immune responses. Recently, Kuga et al. reported that a site- and phosphorylation status–

specific antibody against Girdin is a selective tuft cell marker in the mouse and human GI tract [54]. Identifying GI region-specific chemical coding will be useful for further understanding of the function of tuft cells.

## Links between epithelial sensory cells and neuronal pathways

Afferent neuronal pathways contribute towards luminal chemosensing that regulates GI function, in addition to transmitting satiety signals and visceral sensations to the central nervous system. Extrinsic afferent nerves originating in the nodose ganglia densely innervate the antrum and duodenal lamina propria [55] and also in the lumen of lymphatic lacteals [56]. Williams et al. recently demonstrated that GLP-1 receptor-expressing nodose neurons were mostly stretch sensors innervating the stomach, whereas the GPR65-expressing population innervated duodenal villi and responded to luminal nutrients [57**]. In addition to specific receptors associated with EEC-released hormones such as 5-HT, CCK, and GLP-2, afferent neurons possess nutrient receptors, including LPA5, mGluRs, and FFA3 [56;58;59]. Sensory nerves in the subepithelial space likely receive EEC signals and directly detect absorbed nutrients.

Similar to taste cells present in the lingual taste buds, EECs and tuft cells may communicate with afferent nerves. Indeed, pre- and post-synaptic markers are expressed in these cells [38;60]. PGP9.5-positive nerves directly contact some duodenal tuft cells, which are labeled by the fluorescent probe TRPM5-GFP [38]. Bohorquez et al. demonstrated the development of EEC-neuronal connections using 3D imaging in vivo, and further documented the formation of connections between isolated CCK-GFP cells and co-cultured sensory neurons in vitro by video capture [60]. Takahashi et al. demonstrated that the epithelial muscarinic ACh receptor antagonist upregulates and its agonist downregulates organoid growth, suggesting that neural and non-neural cholinergic signals modulate epithelial cell differentiation and that epithelial ACh may be a transmitter from epithelial cells to neurons [61].

The TRPV1 activator capsaicin is used to selectively de-afferent experimental models of neural function. Glucose transporter (SGLT1) upregulation induced by a 3-hour jejunal luminal perfusion of glucose is blocked by capsaicin deafferentation [62], suggesting that the TRPV1-expressing afferent neural pathway is required for the acute epithelial adaptation to luminal nutrients.

## Duodenal anion secretion is mediated by EECs and by afferent neuronal pathways

Our group has investigated how capsaicin-sensitive afferent nerves contribute to duodenal mucus secretion induced by luminal acid and mGluR4 agonists [63;64]. We recently reported that the rat proximal duodenum possesses an active short-chain fatty acid (SCFA) absorption mechanism and that luminal SCFAs stimulate duodenal bicarbonate secretion via SCFA receptors (FFA2 and FFA3) and SCFA transporter-dependent pathways (Figure 2) [65;66]. Luminal SCFA acetate increases the secretory rate of bicarbonate through FFA2-mediated 5-HT release and FFA3-mediated GLP-2 release, consistent with results of studies in which selective FFA agonists were used singly [23;67*]. Since the response to acetate is significantly reduced by SCFA transporter inhibition or by capsaicin deafferentation [66],

afferent nerves may detect SCFA directly after absorption and potentiate EEC transmitter release to increase duodenal mucosal protection.

Xenin, an anorectic hormone, is produced in the brain and in duodenal EECs. Plasma xenin concentrations are increased by meal ingestion or sham feeding in humans, suggesting that vagal reflexes stimulate xenin release from the duodenal mucosa [68]. The infusion of low concentrations (4–12 pmol/kg) of xenin to humans delays gastric emptying, inhibits GLP-1 release, and causes mild diarrhea [69;70]. Since RYGB obesity surgery diminishes exogenous xenin-associated diarrhea and the inhibition of GLP-1 release in response to liquid meal, duodenal xenin signals may significantly activate unknown neural pathways [71*]. Intravenous xenin stimulated duodenal bicarbonate secretion in vivo, and basolateral xenin induced chloride secretion via an afferent neural pathway involving NTS1, NK1, and 5-HT3 receptors in Ussing chambered rat duodenum [21**]. These observations suggest that duodenal xenin activates afferent neural pathways and that the neurotransmitter releases from afferent nerves are likely preserved in isolated intestinal segments. The function of afferent nerves innervating the duodenal mucosa may not be limited to transmitting post-prandial signals to the central nervous system, but may also be involved in the regulation of postprandial mucosal defenses.

### Conclusion

Luminal nutrients activate mucosal sensory cells such as EECs and tuft cells, and afferent nerves through specific GPCRs and transporters before and after absorption. The population of EECs and tuft cells are altered by luminal environmental change or mucosal abnormality, suggesting that they have the potential to be disease markers. Understanding GI chemosensing functions opens the possibility that a variety of nutrient GPCRs are potential drug targets for modulating epithelial cell proliferation, GI physiological function, and also metabolic control.

## Acknowledgments

*Financial support:* Department of Veterans Affairs Merit Review Award

The authors thank Ms. Stacy Jung for her expert administrative assistance.

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**Key points**

- A variety of nutrient G protein-coupled receptors (GPCRs) are differentially expressed in enteroendocrine cells (EECs) and in tuft cells of the gastroduodenal mucosa.
- The population of EECs and tuft cells are altered by bariatric surgery, functional dyspepsia, or mucosal inflammation.
- Luminal nutrients regulate gut hormone releases via GPCR activation and transporter-dependent mechanisms.
- Postprandial duodenal anion secretion is stimulated by luminal and absorbed nutrients via EEC and afferent neural activations.

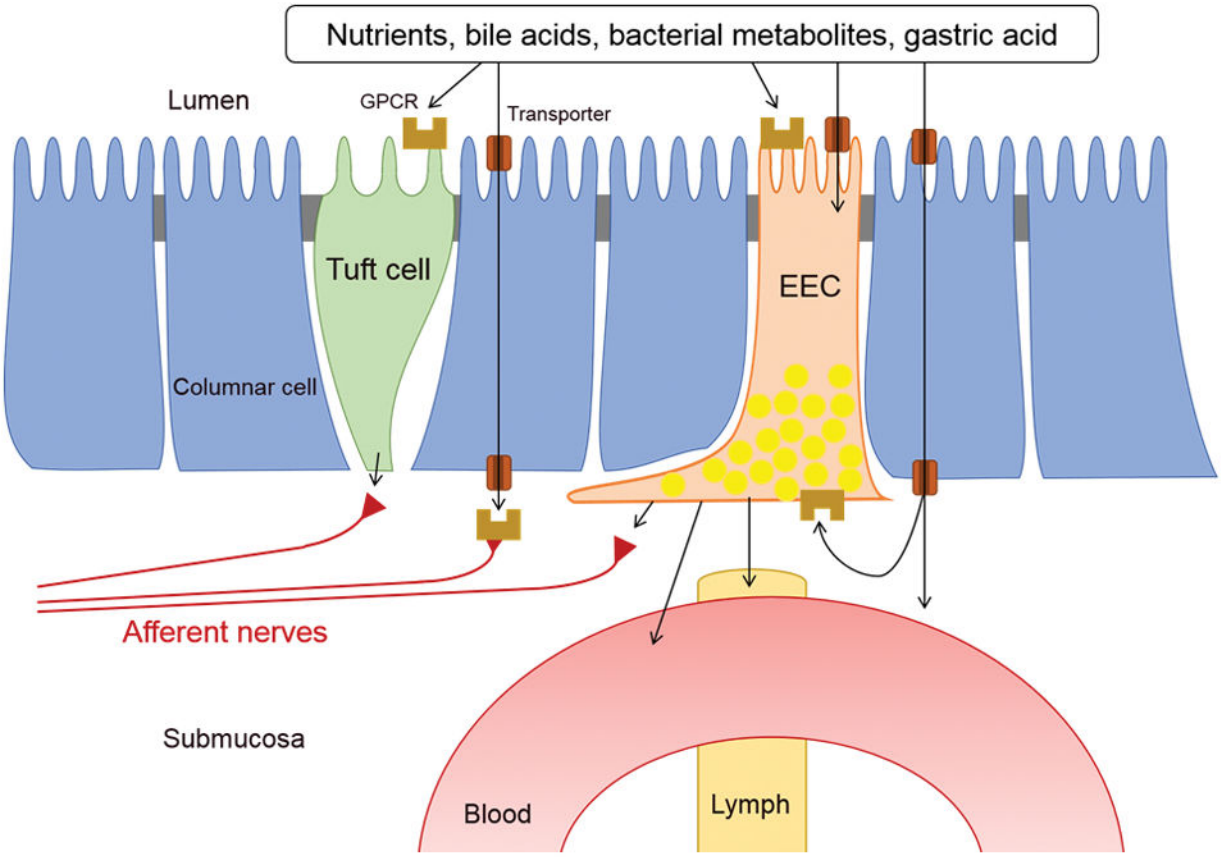


**Figure 1.**

Luminal chemosensing cells in GI, including tuft cell, enteroendocrine cell (EEC), and afferent sensory neurons. A variety of GPCRs are expressed on the sensory cells, activated by luminal solutes before and after absorption through specific transporters. Sub-epithelial afferent nerves may directly receive signals from tuft cells and EECs.

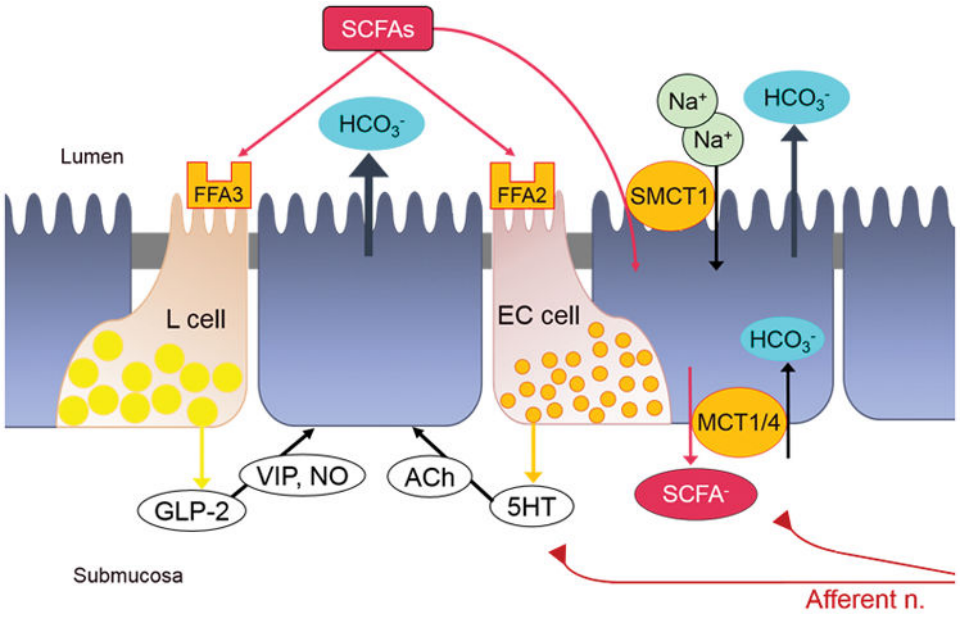


**Figure 2.**

SCFA-activating duodenal bicarbonate secretion (DBS). FFA3 activation stimulates GLP-2 release, followed by vasoactive intestinal peptide (VIP) and nitric oxide (NO) releases, increasing DBS. FFA2 activation stimulates 5-HT release, which activates cholinergic pathway to stimulate DBS. Sodium-dependent and independent monocarboxylate transporters SMCT1, MCT1, and MCT4 mediate SCFA absorption, facilitating DBS via afferent neural pathways.