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Recent Advances in Gut Nutrient Chemosensing

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Abstract

The field of gut nutrient chemosensing is evolving rapidly. Recent advances have uncovered the mechanism by which specific nutrient components evoke multiple metabolic responses. Deorphanization of G protein-coupled receptors (GPCRs) in the gut has helped identify previously unliganded receptors and their cognate ligands. In this review, we discuss nutrient receptors, their ligand preferences, and the evoked neurohormonal responses. Family A GPCRs includes receptor GPR93, which senses protein and proteolytic degradation products, and free fatty acid-sensing receptors. Short-chain free fatty acids are ligands for FFA2, previously GPR43, and FFA3, previously GPR41. FFA1, previously GPR40, is activated by long-chain fatty acids with GPR120 activated by medium- and long-chain fatty acids. The GPR119 agonist ethanolamide oleylethanolamide (OEA) and bile acid GPR131 agonists have also been identified. Family C receptors ligand preferences include L-amino acids, carbohydrate, and tastants. The metabotropic glutamate receptor (mGluR), calcium-sensing receptor (CaR), and GPCR family C, group 6, subtype A receptor (GPRC6A) mediate L-amino acid-sensing. Taste receptors have a proposed role in intestinal chemosensing; sweet, bitter, and *umami* evoke responses in the gut *via* GPCRs. The mechanism of carbohydrate-sensing remains controversial: the heterodimeric taste receptor T1R2/T1R3 and sodium glucose cotransporter 1 (SGLT-1) expressed in L cells are the two leading candidates. Identification of specific nutrient receptors and their respective ligands can provide novel therapeutic targets for the treatment of diabetes, acid reflux, foregut mucosal injury, and obesity.

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Keywords

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INTRODUCTION

Multiple metabolic responses, including the release of hormones within the gastrointestinal (GI) tract, occur after ingestion of a meal. Furthermore, specific macronutrient and micronutrient components elicit individual mucosal responses [1]. Numerous hypotheses have since been proposed regarding the mechanism of nutrient chemosensing. Research in this field picked up momentum in the mid to late 1990s: Layer and colleagues reported in 1995 that ileal carbohydrate and lipid perfusions evoked the release of glucagon-like peptide 1 (GLP-1), a hormone known at that time to regulate gastric secretion [2]. Dumoulin and colleagues reported in 1998 the hormonal responses to infusions of individual nutrients in the vascularly perfused rat ileum in comparison to earlier studies of mixed meals, measuring the release of the hormones peptide tyrosine-tyrosine (PYY), GLP-1, and neurotensin (NT). These hormones are involved in the “ileal brake”, a negative feedback mechanism that slows motility in response to unabsorbed nutrients. GLP-1 was released in the presence of glucose, peptones, the short-chain fatty acids propionate and butyrate, the long chain fatty acid oleate, and taurocholate, a major bile salt in rats (Fig. 1). Notably, relatively high concentrations of each nutrient ligand were needed to evoke peptide release. The “ileal brake” regulates digestion and absorption when luminal contents make contact with the L and N cells of the gut mucosa from which hormones are released. Dumoulin and colleagues suggest the “ileal brake” mechanism optimizes late postprandial regulation in states of maldigestion or malabsorption [3].

Until recently, the mechanism by which luminal nutrients evoke hormone release has been poorly understood. Recently, nutrient-sensing G protein-coupled receptors (GPCR) were localized to the enteroendocrine plasma cell membranes at the brush border, facing into the gut lumen, activated by post-prandial luminal contents [4, 5]. Ligands for these nutrient-sensing GPCRs include the nutrients previously reported to elicit gut hormone secretion (Fig. 1). Induced by luminal ligand stimuli, the GPCRs G_q and G_s elevate intracellular calcium (Ca^{2+}) concentrations and promote cAMP generation, respectively [6, 7]. Initiation of signaling cascades increases intracellular cAMP or Ca^{2+} concentration which trigger peptide hormone release [4].

Identification of the enteroendocrine cells on which these GPCRs are located has enabled identification of specific nutrient sensor-expressing epithelial cells. Engelstoft and colleagues summarized sensory and secretory functions of enteroendocrine cells in the gut in 2008 [5] (Fig. 2).

In this review, we will discuss the evolution and briefly summarize the current state of gut nutrient sensing, highlighting nutrient-sensing specific GPCRs.

ENTEROENDOCRINE CELLS

There are at least fourteen different endocrine cell types of the GI tract, each with its own regional distribution and each releasing a specific hormone in response to local stimuli (Fig. 2). Entero-endocrine cells of the open type are conical in shape with microvilli extending into the gut lumen. Peptide hormones are secreted from secretory granules, located at the base of the cell. They are scattered among mostly non-endocrine mucosal cells, including absorptive enterocytes and goblet cells, within the lining of the gut epithelium. Enteroendocrine cells I, K, and L are of particular relevance because of the hormones they release. Enteroendocrine I-cells are responsible for synthesizing and secreting cholecystokinin (CCK) into the submucosal space. CCK is released in response to fatty acids with carbon chain length greater than 12 [8, 9]. Functions of CCK include stimulation of pancreatic enzymes, contraction of the gallbladder to release bile salts, and satiety through slowing of gastric emptying [8]. K-cells are located in the upper small intestine whereas L-cells are located in distal intestine. K and L-cells are responsible for producing the incretins glucose-dependent insulinotropic peptide (GIP) and GLP-1, respectively, which have gained attention for their central role in glycemic control and obesity [10]. Food intake and satiety may be mediated by GLP-1 due to its inhibitory effect on gastric emptying, suppression of glucagon secretion, or its regulatory role in postprandial insulin secretion. GIP affects lipid metabolism and fat delivery to adipose tissue [8]. L-cells are also responsible for producing GLP-2, involved in the repair of the intestinal epithelium, and PYY, involved in delayed gastric emptying [11, 12].

Isolation of Enteroendocrine Cells via Fluorescence Activated Cell Sorting

Identification of previously unliganded GPCRs, also known as orphan receptors, and their cognate ligands has been made possible due to fluorescence activated cell sorting (FACS) which was used to isolate and identify a pure population of cells [5]. Reimann and colleagues isolated purified L-cells from mice in which the proglucagon promoter was used to selectively express Venus fluorescence in L cells. They reported that this L cell population expressed several deorphanized nutrient sensing GPCRs such as FFA1, FFA2, FFA3, GPR119, GPR93, and GPR131, and the sodium-coupled glucose cotransporter-1 (SGLT1) transporter, was electrically excitable and nutrient, particularly glucose, responsive. They suggest the signaling cascade is regulated by sodium glucose cotransporters (SGLTs) and ATP-sensitive potassium (K_{ATP}) channels [13]. Meanwhile, Samuel and colleagues reported the contribution of GPR41 in the hormonal response to short-chain fatty acids in the ileum and colon. Utilizing FACS, purified CCK-positive cells were isolated from transgenic mice in order to test peptide production based on the location of the CCK-receptor. GPR41-deficient mice exhibited decreased PYY secretion and hepatic lipogenesis, consistent with decreased absorption of short-chain fatty acids due to GPR41-deficiency, as discussed below [14]. GPR41 is also referred to as FFA3.

Taste Receptors

Many deorphanized GPCRs were determined to be taste receptors. Mammalian taste receptors are distributed in clusters of 50–150, forming taste buds primarily on the lingual epithelium [15, 16]. The five basic tastes include sweet, salty, bitter, sour, and *umami*

(savory), each mediated by its own signal transduction pathway [17]. Oral taste receptors have a primary role in the evaluation and selection of food, palatability, and satiation [18]. Tastants refer to compounds which are able to evoke similar responses as the five basic taste modalities. For example, the artificial sweetener sucralose and monosodium glutamate are tastants that trigger oral receptors for sweet and *umami*, respectively. Tastants have the ability to regulate the activity of ion channels that mediate increases in intracellular Ca^{2+} concentrations; this subsequently initiates the release of peptides [19]. Taste receptors have garnered attention in concurrent research over the last decade for their role in nutrient chemosensing within the gut. Sweet, bitter, and *umami* evoke responses in the gut *via* GPCRs [20]. Recent studies suggest subunits of taste receptor pathways are expressed in intestinal cells. Intestinal expression of the specific heterotrimeric G protein gustducin was the first indication that taste receptors are present in the gut. Gustducin may regulate postprandial gut GLP-1 and hormone release [21–23]. Jang and colleagues reported the mechanism of glucose-sensing in the gut lumen based on GLP-1 response in the L cell [23]. In the lingual epithelium, type 1 taste GPCRs (T1Rs) heterodimerize to form T1R2/T1R3 which is activated by sweet compounds [24–26]. This activation couples with the gustducin which then mediates second messenger signaling cascades [27]. Alpha-gustducin (α -gustducin) is a key subunit of gustducin, coexpressed in GIP expressing K-cells and GLP-1 L-cells throughout the stomach and intestine [23, 28]. The term *umami* is derived from the Japanese word for savory used to describe the taste of L-glutamate. Purine ribonucleotide monophosphates such as inosine monophosphate (IMP) and guanosine monophosphate (GMP), though unable to evoke *umami* taste alone, can synergistically increase the characteristic taste of glutamate. Li and colleagues reported the *umami* tastant L-glutamate combined with 5'ribonucleotide monophosphates evoke responses from T1R1/T1R3, a member of the type 1 taste receptor family [29]. Zhang and colleagues reported glutamate recognition and enhancement by IMP using sweet-*umami* chimeric receptors, mutagenesis analysis, and molecular modeling. One of the few naturally allosteric modulators for GPCRs, IMP binds near glutamate, stabilizing the outer membrane N-terminal Venus flytrap domain of T1R1 [30]. The gustducin-coupled pathway is the common link joining sweet and bitter sensing [27, 31]. Type 2 taste GPCRs (T2Rs), the second family of taste receptors identified, have a sensitivity for bitter compounds [32]. At this point, there appears to be multiple bitter taste receptors. This area, recently reviewed by Andrew-Barquin and Conte [33], continues to evolve rapidly.

G PROTEIN-COUPLED RECEPTORS AND LIGAND PREFERENCES

Although the number of GPCRs in the human genome runs into the hundreds, they nonetheless may be separated into five families based on sequence homology and functionality [34, 35]. This classification system is termed GRAFS, an acronym for each family of proteins: glutamate, rhodopsin, adhesion, frizzled, and secretin [34]. The rhodopsin receptors, also known as Family A, and glutamate receptors, also known as Family C, are of particular relevance with respect to nutrient-sensing [36, 37]. Rhodopsin receptors, the largest class, have ligand preferences for proteins and proteolytic degradation products and fatty acids. Family C receptor ligand preferences include L-amino acids,

carbohydrates and tastants. The mechanism and functionality of specific receptors for proteins, L-amino acids, fatty acids, and carbohydrates will be discussed below.

Protein and Peptide-Sensing Receptors

Choi and colleagues first identified GPR93 in rats and reported that the receptor is directly responsive to protein hydrolysates, a mixture of proteolytic degradation products. GPR93 is highly expressed in the intestinal mucosal layer, especially in the duodenum. Stimulation of this receptor promotes CCK gene transcription and signals release of this hormone [37]. Similarly, Cordier-Bussat and colleagues reported that protein hydrolysates from meat, casein, and soybean stimulated GLP-1 release, in addition to CCK. In contrast, mixtures of free amino acids and undigested proteins did not [38].

L-Amino Acid-Sensing Receptors

Amino acid-sensing receptors include the metabotropic glutamate receptor (mGluR), calcium-sensing receptors (CaR), and GPCR family C, group 6, subtype A receptor (GPRC6A). The former is the only receptor that is amino acid-specific; the other receptors have ligand preferences for groups of amino acids typically based on stereospecificity. In addition to the taste receptor T1R1/T1R3, mGluR1 and 4 are L-glutamate receptors [39]. Akiba and colleagues tested mGluR ligands in order to determine their role in duodenal mucosal defenses. mGluR 4 mediates L-glutamate-induced duodenal epithelial intracellular alkalization, measured *in vivo* and increases mucus gel thickness whereas mGluR 1/5 are partially involved in epithelial cellular alkalization [40]. While pharmacologic evidence and functionality suggest that mGluRs mediate amino-acid sensing, limited data are available regarding their mechanism and expression in epithelial cells. Pepsin is released in response to gastric acid; it is responsible for proteolysis, producing peptides and free aromatic amino acids. Proteolytic products, gastric pH, and intraluminal Ca^{2+} are major stimulants of gastrin release, produced by gastric G cells [41–43]. CaR not only regulates Ca^{2+} homeostasis, but also mediates amino acid-sensing and gastric acid secretion. Feng and colleagues reported CaR is expressed on G cells in the stomach regulating gastrin and acid secretion *in vivo* [44]. Busque and colleagues reported that L-amino acids, in the presence of physiological concentrations of extracellular Ca^{2+} , stimulated gastric acid secretion from parietal cells *via* CaR [45]. The sensitivity of CaR to amino acids, pH, and Ca^{2+} correlate to that of G-cells. This supports the regulatory role of CaR in gastrin release, mediated not only by the direct activation by intraluminal Ca^{2+} but gastric nutrients and intragastric content as well. The insensitivity of G-cells to luminal content and pH in the absence of CaR further supports the receptor's role in gastric acid secretion [46]. Notably, duodenal luminal contents affect gastric acid secretion and inhibition. Akiba and colleagues reported CaR agonists increase mucus gel thickness, blood flow, and bicarbonate secretion in the rat duodenum [40]. The “duodenal brake,” first described by Andersson in 1960, also functions by inhibiting gastric acid secretion and delaying gastric emptying in the presence of intraduodenal acid [47, 48]. These findings may be pertinent to understanding and treating reflux disorders. CaRs appear to be stereoselective, with the most potent antagonists being the aromatic amino acids L-phenylalanine and L-tryptophan; aliphatic and polar amino acids including serine, threonine, glycine, and alanine can also evoke CaR responses [45, 49]. GPRC6A, a recently deorphanized GPCR has reported sensitivity for basic L-amino acids L-

lysine, L-arginine, and L-ornithine [50]. Expression of GPCR6A appears to be high in gastric parietal cells and less endocrine cells [51]. Much is still unknown regarding its function in the GI tract and the identity of other potential ligands. The role of oral taste receptor heterodimer T1R1/T1R3 in luminal amino acid-sensing remains debatable [52]. Akiba and colleagues reported the presence of T1R1/T1R3 in the duodenum as copreparation of amino acids L-aspartate, L-leucine, and L-alanine with IMP increasing HCO_3^- secretion; this reaction echoes that of L-glutamate and IMP [30, 52]. Further developments in this subject are hindered by the lack of specific antibodies and selective agonists and antagonists for these receptors in the GI tract [53]. Future studies may uncover mechanisms for sensing all twenty L-amino acids.

Free Fatty Acid-Sensing Receptors

In addition to intracellular metabolism, fatty acids help regulate basal insulin and act as antagonists of insulin-mediated glucose uptake and glycogenesis [54]. There is also the aforementioned longstanding understanding of the relationship between long-chain fatty acids and CCK release by I cells in the proximal small intestine. In 1984, Hopman and colleagues reported CCK release with subsequent gallbladder contraction in response to administration of oral long-chain triglycerides, but not medium-chain triglycerides, in healthy human volunteers [9]. Short-chain free fatty acids are ligands for FFA2 and FFA3. FFA2 is expressed in the GI tract, adipocytes, and immune cells; it is involved in metabolic homeostasis through inhibition of lipolysis [55, 56]. FFA3 is expressed in the GI tract and adipose tissue. Xiong and colleagues report FFA3 agonists induce leptin release from adipocytes to regulate energy homeostasis [57]. Carboxylate anion length appears to correlate with the potency of ligand activation. As reported by Brown and colleagues, the potency for FFA2 ligand is: acetate (C_2) = propionate (C_3) = butyrate (C_4) > pentanoate (C_5) > hexanoate (C_6) = formate (C_1); potency for FFA3 is: propionate = pentanoate = butyrate > acetate > formate. Saturated and unsaturated fatty acids containing nine or more carbon atoms did not activate FFA2 or FFA3 [58]. FFA1 is activated by longer chain fatty acids, was first reported by Briscoe and colleagues in 2003 using quantitative reverse transcription-PCR to be expressed in the pancreas and in the brain. On the basis of intracellular Ca^{2+} measurements in a heterologous expression system, they reported that a range of medium- and long-chain fatty acids activate FFA1 [59]. Itoh and colleagues report that the expression of FFA1 in pancreatic β -cells suggests a regulatory role in insulin release [60]. FFA1 is expressed in incretin-expressing K and L cells. Edfalk and colleagues reported that FFA1 indirectly regulates insulin release, *via* mediation of incretin release [61]. Observations of pancreatic insulin secretion due to free fatty acid-sensing by FFA1 may give insight into obesity secondary to insulin resistance. The potency of saturated fatty acids were chain-length dependent, as reported in earlier studies regarding FFA2 and FFA3; the most potent were pentadecanoic acid (C_{15}) and palmitic acid (C_{16}). The potency of unsaturated fatty acids did not appear dependent on chain length or the degree of saturation; of all saturated and unsaturated fatty acids tested, 5, 8, 11-eicosatriynoic acid was the most potent. Briscoe and colleagues propose that fatty acid agonists of GPR40 may be tissue-dependent [59]. GPR120 is activated by medium- and long-chain free fatty acids. GPR120, expressed abundantly in the intestine, has ligand preferences for saturated free fatty acids with chain length C_{14} to C_{18} and unsaturated free fatty acids with chain length C_{16} to C_{22} [62].

GPR120 promotes the release of the incretins GIP and GLP-1 [63, 62]. It also mediates CCK release in murine-derived enteroendocrine STC-1 cells, as reported by Sidhu and colleagues [64], as reviewed by Hara and colleagues [65]. Overton and colleagues identified the fatty acid ethanolamide oleoylethanolamide (OEA) as the primary ligand for GPR119 [66]. GPR131, also known as Gpbar1, a bile acid receptor, was first cloned in 2002 by Maruyama and colleagues [67]. GPR131 is expressed in enteroendocrine cells, such as STC-1, with a particularly high mRNA expression in the ileum and colon of mice. It is believed that bile acids stimulate GLP-1 release *in vivo* with GPR131 acting as the intermediary [68, 69].

Carbohydrate-Sensing Receptors

Early studies reported increased plasma concentrations of the incretins GIP and GLP-1 following oral ingestion of glucose, whereas no effect was seen following intravenous injections of glucose. This observation confirmed the ability of the gut lumen to detect glucose in order to initiate glycemic regulation [70]. Though glucose ingestion is believed to trigger the release of incretin hormones in order to maintain glucose homeostasis, the mechanism of glucose chemosensing in the gut lumen remains unknown.

As described above, the heterodimeric receptor T1R2/T1R3 has a proposed role as a taste receptor and as a gut carbohydrate sensor [23, 71]. Jang and colleagues compared release of GLP-1, GIP, and insulin in response to gavage-administered glucose into the stomachs of α -gustducin null and wild-type homozygous mice. Plasma concentrations of GLP-1, GIP, and insulin were absent or did not achieve the same rise in the α -gustducin null mice vs. wild-type. A duodenal infusion of 10% glucose did not evoke GLP-1 release in α -gustducin null mice indicating that luminal sensing is present in the duodenum. Jang and colleagues reported that glucose stimulates a signaling pathway in the gut lumen which mirrors that which occurs in the lingual epithelium [23]. T1R2/T1R3 has a broad sensitivity for natural sweet substances, such as sucrose and sweet-tasting D-amino acids, in addition to artificial sweeteners [26]. In FACS-purified L cells, Reimann and colleagues reported that despite oral taste receptor sensitivity to artificial sweeteners, acesulfame potassium (acesulfame K) and sucralose did not evoke GLP-1 release from L cells at low concentrations. Only higher millimolar concentrations evoked a response, suggesting an independent pathway for GLP-1 release [72]. Fujita and colleagues reported that oral gavage of the artificial sweeteners saccharin, acesulfame K, D-tryptophan, sucralose, and stevia did not release incretins in Zucker diabetic obese rats. Artificial sweeteners also did not improve glycemic control compared to an oral glucose load during an intraperitoneal glucose tolerance test [28]. The inability of artificial sweeteners to trigger enteroendocrine hormone release in order to achieve glucose homeostasis does not support direct intestinal glucose sensing *via* sweet taste receptors.

More recent studies have focused on the function of SGLT-1 in L cells as a more likely receptor than T1R2/T1R3. SGLT-1 has accepted function in glucose homeostasis as it is the main transporter of exogenous sugars from the intestinal lumen into enterocytes [73, 74]. Moriya and colleagues reported the potential role of SGLT-1 in the mechanism of glucose-induced incretin release *in vivo* in mice. SGLT-1 mRNA is highly expressed in the upper and middle small intestine, moderately in the lower small intestine, and minimally in the colon.

Notably, whereas perfusions of glucose administered into the upper intestines of mice triggered incretin hormone release, no response was detected in the colon with the same perfusion, consistent with SGLT-1 mRNA localization. Administration of the nonmetabolizable SGLT-1 substrates α -methyl-D-glucopyranoside (MDG) and 3-*O*-methyl-D-glucose demonstrated that sodium ions and glucose analogs are independently able to trigger incretin release *via* SGLT-1 without the need for glucose metabolism [63, 75]. Conversely, intraluminal coadministration of the SGLT-1 inhibitor phloridzin and glucose blocked glucose absorption and incretin release. Oral MDG significantly increased GIP, GLP-1, insulin, and overall decreased plasma blood glucose levels in the hyperglycemic state. Moriya and colleagues work supports SGLT-1 as a primary gut glucose sensor underscoring its essential role in glucose-induced incretin release [75]. To verify sweet taste receptor effects on incretin hormone release, Moriya and colleagues did not report a marked increase in incretin release following administration of saccharin and sucralose [75]. Margolskee and colleagues reported sucralose was able to trigger SGLT-1 mRNA and improve glucose uptake in wild type mice but not T1R3 or α -gustducin null mice; this is suggestive of an indirect pathway *via* stimulation of sweet taste receptors [76]. The mechanism of glucose chemosensing in the gut lumen *via* direct or indirect SGLT-1 stimulation remains controversial, particularly with regards to GLP-1 release.

CLINICAL IMPLICATIONS

Numerous novel treatments can benefit from increased understanding of the mechanism of nutrient chemosensing. New therapeutic targets can be found with the identification of specific nutrient receptors and their respective agonists and antagonists.

Type 2 Diabetes

Understanding the mechanism of glucose-induced incretin release could provide the basis for significant advances in the treatment of type 2 diabetes. Since type 2 diabetic patients exhibit decreased GLP-1 secretion and insulinotropic effect of GIP [77], novel therapeutic targets are focused on promoting incretin release. Existing treatments, which include incretin mimetics acting as receptor agonists or as incretin enhancers, are not aimed at the release mechanism. Due to the short plasma half-life incretins, enzyme inhibitors such as dipeptidyl peptidase IV (DPP-IV) inhibitors prevent degradation of incretin hormones [78]. Incretin-releasing nutrient GPCRs are new molecular targets for future drugs used for diabetes treatments. Although traditionally carbohydrates were used to evoke incretin release, many other nutrient ligands can also stimulate release (Fig. 1). Moriya and colleagues propose noncalorigenic SGLT-1 substrates as a novel treatment as they have the ability to treat hyperglycemia by stimulating the release of incretin hormones [75].

Acid Reflux

CaR may be a useful molecular target in the treatment of acid reflux disorders. The drugs are already in clinical practice as calcimimetics and calcilytics used to regulate Ca^{2+} homeostasis in renal failure. Given orally, similar drugs could be used to regulate gastric acid secretion [79]. As discussed, orally ingested Ca^{2+} induces gastrin secretion in humans *via* gastric and duodenal sensors [80]. Feng and colleagues tested this response in wild-type,

heterozygous, and CaR-null mice. Gastrin release in CaR-null mice was minimal with administration of gavage Ca^{2+} compared to wild-type and heterozygous mice where a more significant response was noted [44]. The CaR response to calcium carbonate-containing antacids, calcilytics, and calcimimetics may provide additional insight into pharmaceutical treatment of acid-peptic disorders.

Mucosal Defenses

The foregut mucosa, continually exposed to ingested foodstuffs, extremes of luminal pH (ranging from 1–8), and noxious compounds has evolved robust protective defense mechanisms. Of these, epithelial bicarbonate secretion, mucus secretion, cellular pH regulation, and mucosal blood flow, are all responsive to luminal acidification [81, 82]. Luminal pH sensing of the duodenal mucosa has been attributed to multiple interconversions of H^+ and CO_2 , facilitated by soluble and membrane-bound carbonic anhydrase, with transepithelial movement as CO_2 , akin to the Jacobs-Stewart cycle of red cells [83–85]. An ecto-puriner mechanism was described wherein the pH-dependent hydrolytic activity of brush-border alkaline phosphatase serves as a pH sensor regulating surface layer pH and [ATP] [86–88]. Most recently, as mentioned above, Akiba and colleagues reported that the nutrient glutamate is sensed by a variety of mechanisms, including the *umami* taste receptor, the CaR, and mGluR [40]. Preliminary data suggests that luminal glutamate evokes GLP-2 release which releases vasoactive intestinal peptide (VIP) from enteric nerves which increases the rate of bicarbonate secretion. It is likely that other nutrient sensor ligands are capable of enhancing mucosal defenses as well.

Obesity

Appetite regulation and therapeutic targets for obesity may also benefit from understanding how nutrient receptors mediate satiety. The peptides with the most profound effect on satiety are CCK, PYY, GLP-1, and ghrelin. As mentioned, the activation of GPCRs by free fatty acids triggers the release of peptide CCK which inhibits gastric emptying and increases stomach distension. Similarly, GLP-1 also acts as a negative feedback signal *via* the aforementioned “ileal brake” [18, 89]. In addition to reporting the role of GPR119 in mediating the response to endogenous fatty acid OEA, which reduces food intake in rodent feeding models, Overton and colleagues identified small-molecule GPR119 agonists as novel pharmaceutical interventions for obesity. OEA and the optimized GPR119 agonist PSN632408 reduced food intake in fasting and diet-induced obese rats. Mean weights, measured by change in white adipose tissue depots, also decreased [66]. Modulation of peptide targets *via* nutrient receptors can shed new light on appetite regulation and interventions for obesity.

SUMMARY

Over the last decade, major shifts have occurred in the understanding of the mechanism regarding nutrient sensing, stemming from the deorphanization of previously unliganded receptors and the FACS-assisted purification and characterization of enteroendocrine cells. This review discussed specific GPCRs responsible for the chemosensing of proteins, L-amino acids, bile acids, fatty acids, and carbohydrates. Identification of nutrient receptor

agonists and antagonists can provide novel therapeutic targets for the treatment of diabetes, acid reflux, mucosal injury, and obesity.

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Fig. (1).
Effects of luminal administration of individual nutrients on the release of GLP-1 in the isolated rat ileum preparation as reported by Dumoulin and colleagues in 1998. Specific GPCRs are noted with their cognate nutrient ligand. Adapted from: [3].

Fig. (2). Overview of sensory and secretory functions of enteroendocrine cells of the gut. Adapted from Engelstoft *et al*, Cell Metab 8:448, 2008 [5]. Sodium-glucose cotransporter (SGLT-1) is the main transport of sugars from the intestinal lumen into enterocytes and regulates signaling cascades involved in glucose homeostasis Adapted from: [90].