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Nutrient sensing in the gut: new roads to therapeutics?

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Abstract

The release of gut hormones involved in the control of food intake is dependent on the acute nutritional status of the body, suggesting that chemosensory mechanisms are involved in the control of their release. G-protein coupled taste receptors similar to those in the lingual system that respond to sweet, bitter, umami and fatty acids, are expressed in endocrine cells within the gut mucosa and coordinate together with other chemosensory signaling elements the release of hormones that regulate energy -and glucose homeostasis. In health, these nutrient sensors are likely to function as inhibitors to excessive nutrient exposure and their malfunction may be responsible for a variety of metabolic dysfunctions associated with obesity, thus they may be considered as new therapeutic targets.

Keywords

Taste: a measure of nutritional qualities of foods

Taste is the sensory modality designed to inform us about the nutritional qualities of the food we eat. For humans this means distinguishing the five basic tastes: sweet, salt, umami, bitter and sour. Sweet foods signal the presence of carbohydrates that serve as an energy source. Salty taste governs the intake of Na^+ and other salts, essential for maintaining the body's water balance. Umami taste is associated with protein-rich foods. Bitter taste is innately aversive and protects against consuming poisons. Sour taste signals the presence of dietary acids that are present in spoiled foods and unripe fruits. In the past, the recognition of fat stimuli was believed to rely mostly on textural, olfactory, and post-ingestive cues but the finding that lipid sensors exist on the tongue suggests that fat can be considered as the sixth taste [1].

Map of chemosensory cells in the tongue

Gustatory processing is first achieved at the level of taste receptor cells (TRCs) which are clustered in taste buds on the tongue. Once activated by tastants, TRC transmit the information via sensory afferent fibres to certain brain areas involved in taste perception. Taste cells are classified into four types depending on their morphological features [2]. Salty taste is transduced by some Type I glial-like cells. Type II cells express G-protein-coupled receptors (GPCRs) to sense sweet, umami and bitter foods. Type III cells express channels to sense acids, while Type IV cells are thought to be taste stem/progenitor cells. Two classes of taste GPCRs have been identified; the taste 1 receptor family (TAS1R) and the taste 2 receptor family (TAS2R). Subtypes of the TAS1R family heterodimerize to detect sweet (TAS1R2-TAS1R3) and umami tastants (TAS1R1-TAS1R3) [2] whereas the TAS2R receptor family consists of more than 25 members in humans and detects bitter compounds [3]. The fat-sensing receptors, FFAR1 and GPR120 are expressed in type I and type II cells respectively [4].

α-gustducin, the α-subunit of the G-protein coupled to taste receptors, plays a role in both bitter, sweet and at least partially in umami taste transduction [5, 6]. However α-gustducin$^{-/-}$ mice are not completely unresponsive to bitter and sweet compounds, suggesting the involvement of additional G-proteins which may include members of Gαi subfamily such as transducin, Gαi1 and Gα0 [6, 7]. Besides α-gustducin, which affects cAMP and cGMP levels, a significant role in taste signaling is taken on by the βγ partners (β$_3$γ$_{13}$) of gustducin, which activate phospholipase C$_{\beta2}$ (PLC$_{\beta2}$) [2]. This leads to IP$_3$-mediated release of intracellular Ca^{2+} and activation of the transient receptor potential cation channel subfamily M member 5 (TRPM5). These events lead to membrane depolarization, action potentials and release of ATP, which acts on purinergic receptors to activate gustatory afferents [2].

Map of chemosensory cells in the gut

The gastrointestinal (GI) system as a sensory organ

The idea that the GI system is a sensory organ became evident when Bayliss and Starling [8] discovered the first gut hormone, secretin, and observed that it was released by luminal acid. Later, it became clear that the GI tract responds to a large array of signals in the lumen, including nutrient and non-nutrient chemicals, mechanical factors and microorganisms. The recent progress in unraveling the nutrient sensing mechanisms in the taste buds of the tongue has triggered studies on the existence and role of

chemosensory cells in the gut. Molecular sensing by GI cells plays a crucial role in the control of multiple functions during digestion, and initiates hormonal and neural responses as well as changes in mucosal ion transport that regulate motility, appetite, insulin secretion etc. [9]. Luminal sensing is also critical for initiating the correct response, like mucus secretion or emesis, towards harmful ingested compounds. A prerequisite of chemosensory cells is that they should have direct access to the luminal content. Vagal sensory afferents in the lamina propria never enter the epithelial layer, and thus must sense nutrients indirectly via signals released from the epithelium, such as enterocytes, brush cells and enteroendocrine cells (EECs) [10]. A simplified illustration of the chemosensory signaling pathways in the gut is shown in Figure 1.

Chemosensory signaling in the intestinal epithelium

Enterocytes are absorptive cells that contain microvilli in their apical domain to increase contact with the lumen. They are rich in transporters which enhance uptake of sugars, fatty acids and amino acids from the lumen. A special type of enterocytes is the brush cell, which similar to the TRCs of the tongue, exhibits apical microvilli with long rootlets, lacking intracellular secretory vesicles typical of EECs. Brush cells are considered members of a larger family of solitary chemosensory cells that are also found in the nasal cavity [11]. They express gustatory signalling elements such as α-gustducin [12-18], α-transducin [18] and TRPM5 [13, 15] in several regions of the gut (Table 1) but are highly expressed at the joint (limiting ridge) where food passes from the fundus to the corpus, where digestive processes are initiated [15].

EECs represent less than 1% of the epithelial population, but nevertheless constitute the largest endocrine organ of the human body. More than 20 different EECs produce and secrete a variety of hormones, including gastrin (G-cells), ghrelin (P or X/A-cells), somatostatin (D-cells), cholecystokinin (CCK) (I-cells), serotonin (enterochromaffin (EC)-cells), glucose-dependent insulinotropic peptide (GIP) (K-cells), glucagon-like peptides (GLPs) and peptide YY (PYY) (L-cells). Recent studies suggest that the one cell-one hormone concept dogma for EECs is no longer valid and that a lineage of EECs has the ability to co-express members of a group of functionally related peptides [19, 20]. The EECs can be divided into two groups according to their shape and epithelial localization. The 'open type cells' have microvilli that enables them to sense directly the luminal content. This triggers the EECs to release hormones that enter blood vessels, activate extrinsic or intrinsic afferent nerves or other nearby target cells. In contrast, 'closed type cells' do not reach the epithelial surface and can only be indirectly affected through neural pathways or signals emanating from the blood stream.

Several anorexigenic (GLP-1, PYY$_{3-36}$, CCK) and orexigenic (ghrelin) hormones are released from the gut mucosa, in accordance to a fed or fasted state, and play an important role in regulating short-term food intake [21]. The meal-related fluctuations in plasma GLP-1, PYY, CCK levels (postprandial increase), and ghrelin levels (postprandial decrease), are dependent on the caloric value and the macronutrient composition of the meal [22], that in turn must be monitored by chemosensory mechanisms. α-gustducin-positive cells are co-localized with GLP-1 and PYY containing L-cells, GIP-containing K-cells, and with ghrelin containing X/A-cells of the stomach which are also immunoreative for α-transducin (Table 1) [14, 17, 23-26]. Other chemosensory signaling elements (PLCβ2, TRPM5 etc.) have also been demonstrated in L-cells [25] and X/A-cells [15] (Table 1). Apart from one study [14], the majority of the studies did not find a co-localization between serotonin receptor 5-hydroxytryptamine receptor (5-HT) containing EC-cells and α-gustducin [12, 15, 23].

Hass et al. [15] suggested that analogous to the TRCs, the brush cells may convey information from the lumen to the "closed" EECs. Indeed, PLCß2 was not detected in α-gustducin-expressing brush cells but in

closed ghrelin cells and on neural fibers, suggesting that the ghrelin cells might receive input from adjoining brush cells [13, 15]. In contrast, in the human gastric mucosa ghrelin cells did not co-localize with PLCβ2 or with TRPM5, but were found in close proximity of these chemosensory cells [27].

Bitter taste receptors in EECs

Bitter taste receptor cells in the tongue work by limiting ingestion of bitter-tasting, potentially toxic compounds. In addition, their expression in enteroendocrine cells, might also play a role in limiting toxin absorption [28] . Indeed, stimulation of the murine L-cell line, STC-1, expressing TAS2Rs with bitter ligands increased the release of the satiety hormones, CCK and GLP-1 [28, 29]. Intragastric administration of bitter agonists was shown to induce c-fos activation of neurons in the nucleus tractus solitarus, likely via release of PYY or CCK from endocrine cells activating CCK_1Rs and Y_2 receptors on vagal afferents [30].

Bitter taste receptors in the gut: a bitter pill to treat obesity?

It is assumed that if chemical senses (smell, taste) which serve as primary gatekeepers to the GI tract fail to prevent ingestion of toxins, the GI tract provides the next tier of defense. The brush cells in the stomach are particularly well positioned to detect ingested bitter tastants, and to induce a repulsive-like behavior. Nevertheless, Janssen et al. [17] showed that intragastric administration of bitter tastants induced the secretion of the hunger hormone ghrelin, resulting in a short-term increase in food intake (Figure 2). Although this seems somewhat counterintuitive, in herbal medicine, bitter herbs are being used to stimulate appetite and improve digestion. The before-dinner drink, or aperitif, had its origin in the Roman practice of drinking wine infused with bitter herbs to help process food more efficiently. This short-term increase in ghrelin release, which may temporarily stimulate appetite, is promptly followed by a profound decrease in food intake, correlating with a decrease in gastric emptying to prevent overeating [17]. *In vitro* contractility studies showed a direct inhibitory effect of bitter agonists on neural contractility of gastric smooth muscle strips. Recently, the presence of TAS2Rs along with α-gustducin was demonstrated on smooth muscle cells of the human airways [31]. Similar to the findings in the gut, bitter agonists induced relaxation of airway smooth muscle strips, an effect mediated via TAS2Rs that induce an IP_3-dependent release of Ca^{2+} that opens large-conductance Ca^{2+}-activated K^+ channels, resulting in membrane hyperpolarization. Furthermore, aerosolized administration of bitter tastants relaxed the airways in a mouse model of allergic inflammation [31]. Although it was originally assumed that TAS2Rs would act to contract the tracheal muscle with consequent shortness of breath to escape from a noxious environment, it now appears that bitter agents may be efficacious bronchodilators for treating obstructive lung diseases. In the gut, a similar inhibitory effect of bitter agents on the contractility of the stomach may prolong the presence of nutrients in the stomach. This can result in early satiety and increase the interval between consecutive meals with an overall reduction in food intake.

The effect of the bitter agonist, denatonium benzoate (DB), on satiation in healthy volunteers has also been investigated. Intragastric infusion of DB, increased satiation and reduced the volume of nutrients ingested upon maximal satiation without inducing symptoms [32]. DB was administered intragastrically, indicating that TAS2Rs on the tongue are mainly involved in the nausea-evoking effects of bitter tastants. Future studies are warranted, also in obese patients, to investigate whether a bitter pill may be a promising tool in weight management. Yajima et al. [33] showed that isohumulones, bitter compounds derived from hops present in beer, improved insulin sensitivity in high fat diet-induced obese mice and in type 2 diabetes patients by activation of peroxisome proliferator-activated receptors (PPARs). In addition, isohumulones also decreased body fat in Japanese subjects with prediabetes [34]. In an Amish family diabetes study it

was shown that a functionally compromised TAS2R9 negatively impacts glucose homeostasis probably by affecting the release of GLP-1 [35]. A role for bitter agonists in the regulation of energy –and glucose homeostasis is emerging and thus in the treatment of metabolic disorders. Future studies are warranted to discriminate between effects mediated by bitter taste receptors on endocrine cells and those mediated by other mechanisms.

Targeting bitter taste receptors: facing the problem

There is no such thing as one bitter taste receptor. In humans, 25 TAS2Rs are involved in bitter taste perception. Furthermore many bitter compounds activate several TAS2Rs, e.g. DB activates 8 receptors, while phenylthiocarbamide (PTC) activates only one [3]. PTC is bitter tasting to most people (tasters) but not to some (none tasters). One single bitter agonist can effect different types of endocrine cells and thus induce the secretion of hormones with different functional effects [17, 29]. In addition, some bitter compounds, e.g. quinine and DB, exhibit pronounced pharmacological activities independent of bitter taste receptors such as direct interaction with Ca^{2+} stores or voltage-gated K^+ channels [36, 37].

On the other hand, and given the marked structural diversity between bitter tastants, the choice of compounds that could be developed for therapeutic applications is extensive. A recent database of bitter compounds (http://bitterdb.agri.huji.ac.il/bitterdb/) was set-up which includes over 550 compounds that were reported to taste bitter to humans [38]. In addition, there are thousands of plant-derived bitter tastants and metabolites that could have favorable therapeutic profiles. Interestingly some plants contain high amounts of structurally very similar bitter compounds but with different toxicity profiles [3]. Screening established cellular models expressing specific TAS2Rs, with the numerous bitter compounds available, may help us to determine new physiological functions and therapeutic applications of extra-oral bitter taste receptors.

Sweet taste receptors in EECs

The idea that the GI tract can sense sweet is derived from the 'incretin effect'. Orally administered glucose elicits much higher insulin secretion via the release of incretin hormones (GLP-1 and GIP), compared with intravenous administration. Sweet taste receptors (TAS1R2-TAS1R3) have been detected in brush cells and endocrine L-cells and X/A-cells [16, 18, 24, 25] (Table 1). Studies in TAS1R2-LacZ receptor knock-in mice showed that TAS1R2 is expressed in small intestine and colon, but not in the stomach [39].

In vitro and *in vivo* studies suggest that the α-gustducin-coupled sweet taste receptor complexes, are involved in incretin hormone release. Indeed, studies with the human L-cell line, NCI-H716, showed that the release of GLP-1 was promoted by sugars and by the non-caloric sweetener sucralose, and was blocked by the sweet receptor antagonist lactisole, or by siRNA targeting for α-gustducin [25]. Similar results were obtained for sucralose-stimulated release of GLP-1 and GIP in the mouse GLUTag cell line [40]. In addition, α-gustducin$^{-/-}$ and TAS1R3$^{-/-}$ mice displayed a major deficit in glucose-stimulated GLP-1 release [25, 41]. Studies in humans confirmed that the glucose-stimulated release of GLP-1 and PYY, but not of CCK, is reduced by lactisole [24, 42]. However, in rats, artificial sweeteners failed to acutely induce incretin release *in vivo* [26]. Similar negative results were reported with sucralose in healthy volunteers [43, 44]. Nevertheless, in an 18 month trial, masked replacement of sugar-containing beverages with non-caloric beverages reduced weight gain and fat accumulation in normal-weight children [45]. Geraedts et al. [41] showed that in contrast to the small intestine, a sweet taste receptor independent mechanism mediates glucose-stimulated GLP-1 release from the colon, via closure of K_{ATP} channels or via the sodium-dependent glucose transporter 1 (SGLT1). Indeed, studies in primary L-cells and in GLUTag cells showed

that glucose-stimulated GLP-1 release is also regulated via K_{ATP} channels and SGLT1 [46, 47]. Mice deficient in SGLT1 exhibit a loss of incretin responsiveness to glucose both *in vitro* and *in vivo* [48]. Glucose transporter 2 (GLUT2) also plays an important role in glucose-induced gut peptide secretion by affecting membrane depolarization through closure of K_{ATP} channels [49]. Furthermore, SGLT-1 and GLUT2 are rapidly upregulated in response to luminal sugars or sweeteners but not in TAS1R3$^{-/-}$ and α-gustducin$^{-/-}$ mice, implying a strong correlation among taste receptor activation and modulation of glucose transporter expression [18, 40].

In obese patients the expression levels of a variety of chemosensory elements in the gastric mucosa such as α-gustducin, PLCβ2 and TRPM5 are increased, whereas TAS1R3 levels are decreased [27]. These changes could be part of an adaptive response mechanism adjusting the GI system to a sustained positive energy balance. The expression levels of TAS1R2, TAS1R3, α-gustducin and TRPM5 are decreased in diabetic subjects with elevated blood glucose concentrations, and in glucose-perfused jejunal loops in mice [50], indicating that intestinal taste signaling is under metabolic and luminal control. In conclusion, novel drugs targeting sweet taste receptors on gut endocrine cells may be useful to reduce the risk of obesity-related type 2 diabetes.

Umami and amino acid taste receptors in EECs

Umami sensing

Umami, after the Japanese word umai (delicious) is considered as the fifth basic taste sensation [51]. There are several reports describing umami chemoreception in the gastrointestinal tract. L-glutamate, an umami tasting stimulus, increased the activity of gastric vagal afferents in rats [52] and stimulated gastric secretion and motility in dogs and humans [53, 54]. Ad libitum ingestion of glutamate reduced weight gain in rats without affecting food intake [52]. Putative receptor candidates for umami signaling are the taste receptor heterodimer TAS1R1-TAS1R3 [55], expressed in brush cells and endocrine L and X/A-cells of the gut [13, 16, 18, 24, 25], and also the metabotropic glutamate receptor [56].

Aromatic and basic amino acid sensing

Another candidate amino acid receptor is the calcium sensing receptor (CaR), which is involved in Ca^{2+} and aromatic L-amino acid signaling. The receptor is expressed in G-cells [57-60], I-cells [61, 62] and D-cells (Table 1) [60]. Oral administration of L-phenylalanine (L-Phe) stimulated gastrin secretion in wild type but not in CaR$^{-/-}$ mice, an effect that was mimicked by the CaR-specific ligand, cinacalcet [58]. Administration of L-Phe, elevated plasma levels of CCK and reduced food intake in humans [63]. Additionally in the L-cell line STC-1, and in naïve intestinal I-cells, aromatic amino acids stimulated CCK release via CaR [61, 62, 64]. Amino acids also affected the release of incretins via the CaR in isolated rat intestinal loops [49]. GPRC6A, a receptor that senses basic amino acids and Ca^{2+}, acts in concert with CaR [65]. The receptor is expressed in gastric antral D-cells and G-cells [59, 60].

Peptone sensing

Peptone, a mixture of enzymatically derived peptide fragments, mimics dietary protein digests in the luminal chyme and is sensed by GPR92 (also named GPR93; LPAR5) [66]. This receptor is expressed in G-cells and D-cells of the stomach [60]. The stimulation of gastrin by peptone was abolished by treatment with a CaR antagonist, and in CaR$^{-/-}$ mice [58]. Peptone also stimulated CCK and GLP-1 secretion [67, 68]. Luminal perfusion of peptone stimulated, via the oligopeptide transporter PepT1, CCK-responsive vagal afferent discharge and inhibited gastric motility [69].

Free amino acids can be absorbed via various amino acid transporters with certain group specificities [70], while di- and tripeptides are taken up by the peptide transporter PepT1. Mace et al. [71] showed that L-glutamate acts via amino acid receptors, and glucose acts via sweet taste receptors, respectively, to coordinate regulation of PepT1 and apical GLUT2 reciprocally, indicating that a taste receptor-coordinated network exists within the GI tract that cross-regulates expression of nutrient transporters.

Collectively these data suggest that sensing of amino acids and protein hydrolysates by endocrine cells in the gut is finely tuned by different receptors and transporters which may play an important role in protein-induced satiety and thus in the development of specific protein diets.

Fatty acid taste receptors in EECs

The gut is exposed to high levels of diet-derived fats that are cleaved by lipases to release FFAs. Medium-chain fatty acids (MCFA) (6 to 12 carbons) are absorbed in the intestine by passive diffusion, while long-chain fatty acids (LCFA) (13 to 21 carbons) are absorbed by the fatty acid transporter CD36 and the fatty acid transport protein 4 (FATP-4). Monocarboxylate transporter isoform-1 (MCT-1) is involved in the colonic absorption of short-chain fatty acids (SCFA) (< 6 carbons). FFAs are sensed by nuclear receptors such as PPARs, but also by a broad range of GPCR.

FFAR1 (GPR40) is activated by MCFA and LCFA. FFAR1 is expressed in many endocrine cells but not in D-cells (Table 1) [72]. In the mouse stomach, FFAR1 colocalizes with the desoctanoyl (inactive form) but not with the octanoyl ghrelin (active form) containing cell population [73]. Oral administration of the FFAR1 agonist, MEDICA 16, did not affect ghrelin secretion *in vivo*. The effect of linolenic acid on the secretion of CCK from isolated I-cells was abolished in cells from FFAR1$^{-/-}$ mice [74]. FFAR1 mediates FFA-stimulated insulin secretion indirectly via the release of incretins, but also directly, since FFAR1 is preferentially expressed in β-cells [72, 75]. Although the role of FFAR1 in short-term stimulation of insulin secretion has been confirmed in several studies, conflicting results have been obtained in FFAR1$^{-/-}$ mice studying the role of FFAR1 in the long-term effects of FFAs [76-78]. Thus since FFAR1 might also mediate the long-term toxicity of FFAs both FFAR1 agonists or antagonists are under development for the treatment of type 2 diabetes [79].

GPR120 is also activated by MCFAs and LCFAs but omega-3 fatty acids have often been the focus as endogenous ligands. GPR120 is expressed in brush cells, X/A-cells and L-cells [73, 80]. Stimulation of GPR120 by FFAs promotes the secretion of GLP-1 and CCK from STC-1 cells, and the secretion of insulin [80, 81]. GPR120 is also expressed in ghrelin containing cells in mouse duodenum and oral administration of the GPR120 agonist, grifolic acid, increased ghrelin secretion (Figure 2) [73]. α-gustducin but not GPR120 is involved in the sensing of octanoic acid from the diet, which is necessary for the octanoylation of ghrelin (Figure 2) [73].

GPR120 is also expressed in differentiated adipocytes and macrophages [82, 83]. Omega-3 FA treatment inhibited inflammation and enhanced insulin sensitivity in wild type but not in GPR120$^{-/-}$ mice on high-fat diet [83]. Thus, GPR120 agonists may not only improve insulin sensitivity but may also reduce obesity-induced inflammation [79]. A recent study showed that dysfunction of GPR120 leads to obesity, glucose intolerance and fatty liver [84]. In addition, GPR120 was significantly overexpressed in adipose tissue and stomach of obese individuals [27, 84]. A non-synonymous mutation (p.R270H) was observed in obese subjects which increased the risk of obesity and inhibited GPR120 signalling, in European populations [84].

SCFAs, the end products of non-digestible carbohydrates metabolized by gut microbiota in the colon, are sensed by FFAR2 (GPR43) and FFAR3 (GPR41) [85]. Both receptors are localized in L-cells but not in 5-HT containing cells [86-88] and trigger the secretion of GLP-1 and PYY [89, 90]. FFAR2$^{-/-}$ and FFAR3$^{-/-}$

mice exhibit reduced SCFA-triggered GLP-1 secretion and a parallel impairment of glucose tolerance [89]. These receptors also mediate the effect of SCFAs on immune cells, adipocytes, pancreatic cells [85].

GPR119 does not bind to FAs directly but to the metabolite oleoylethanolamide, an anorectic cannabinoid, and several other endogenous and food-associated lipid metabolites [91]. The receptor is expressed in L-cells and in the GLUTag L-cell line and affects the secretion of the incretins, GLP-1 and PYY [92-95]. GPR119 expressing L-cells are not polarized and thus can sense luminal as well as blood borne lipid metabolites [93]. GPR119 agonists reduced food intake and body weight in diet-induced obese rats [96] and enhanced glucose-stimulated insulin secretion in control and diabetic, but not in GPR119$^{-/-}$ [97] or PYY$^{-/-}$ mice [93]. The effect on insulin secretion may also involve a direct effect at the level of the β cell which expresses GPR119 [91]. These studies suggest that GPR119 agonists may be promising anti-diabetic drugs.

Different types of fatty acid sensing receptors have emerged as important sensors of FFAs in pancreatic β cells or endocrine cells with promising effects in the control of metabolic homeostasis. Especially FFAR1, GPR120 and GPR119 seem to be promising targets for the treatment of type 2 diabetes.

Concluding remarks

Our understanding of the molecular pharmacology, physiological function and therapeutic potential of extra-oral nutrient sensing receptors is evolving quickly. It is tempting to speculate that obesity and diabetes could be treated by selective targeting of nutrient sensors on endocrine cells to release satiety hormones that are often co-stored in conjunction with insulin from the pancreas, thereby mimicking the physiological effects of a meal and fooling the body that it has eaten. It could represent an alternative treatment to combination therapy with satiation hormones which has been put forward to mimic the effects of bariatric surgery on the remission of type 2 diabetes and body weight loss in obese patients [98]. While most progress has been obtained in the development of FFARs ligands to treat type 2 diabetes, the role of bitter taste receptors in the gut in appetite control is a new field that deserves further investigation. Future studies will show which of these and other gut nutrient receptors prove to be pharmacological targets for the treatment and prevention of obesity and diabetes.

Funding

Glossary

Cholecystokinin (CCK): is a hormone that circulates in different molecular forms (CCK8, CCK33/39, CCK58) and is secreted from the enteroendocrine K-cells in the small intestine in response to fat and proteins. CCK causes the release of digestive enzymes and bile from the pancreas and gallbladder. Apart from its role in digestion, CCK is also a satiety signal that decreases meal size and delays gastric emptying.

Ghrelin: Ghrelin is a 28 amino acid peptide with an octanoyl modification at Ser^3 which is necessary for its biological activity. The enzyme, ghrelin-O-acyltransferase (GOAT), is responsible for the octanoylation of ghrelin. Ghrelin is the only circulating hunger hormone and is released from the enteroendocrine X/A cells in the stomach. Ghrelin levels increase before each meal and decrease thereafter to dictate the timing of the meal. Ghrelin stimulates body weight gain by stimulating food intake, and increasing adipogenesis. Ghrelin is an important gastroprokinetic agent. Ghrelin inhibits glucose-induced insulin release and therefore also plays an important role in the regulation of glucose homeostasis.

Glucagon-like peptide -1 (GLP-1): Processing of proglucagon leads to the formation of GLP-1 in the gut/brain and glucagon in the pancreas. GLP-1 [7-36] amide is the biological active form that is, immediately after its release from the enteroendocrine L-cells in the distal gut, cleaved by dipeptidyl peptidase-4 to an antagonist (GLP-1 [9-36] amide). GLP-1 levels increase after a meal to increase satiety. GLP-1 decreases gastric emptying rate and is an important incretin. GLP-1 mimetics are currently developed and used for the treatment of obesity-related type 2 diabetes.

Gustducin: a G-protein associated with basic taste and the gustatory system. It stimulates diverse pathways and plays a role in the transduction of bitter, sweet and umami stimuli. Gustducin is structurally and functionally similar to the G-protein transducin that is expressed in the retina and functions in phototransduction, suggesting that the sense of taste might have evolved in a similar fashion to the sense of sight.

Peptide YY (PYY): PYY is a peptide of 36 amino acids released from the enteroendocrine L-cells in the distal gut in response to a meal. The peptide is cleaved by dipeptidyl peptidase-4 to PYY_{3-36} that acts as a satiety signal. PYY is an important mediator of the ileal break, a primary inhibitory feedback mechanism that controls transit of a meal through the gut in order to optimize nutrient digestion and absorption.

Taste receptors: Taste receptors are seven transmembrane domain G-protein coupled receptors involved in the sensation of taste. The taste 1 receptor family (consisting of 3 subtypes) is involved in the sensation of sweet and umami, the taste 2 receptor family (consisting of 25 subtypes) in the sensation of bitter. Taste receptors are not only present in taste buds on the tongue but also in cells of the gastrointestinal tract, pancreas, respiratory tract, brain etc. Upon binding of basic tastants such as sweet, bitter, umami or fat, second messenger cascades are initiated that result in the release of peptides or neurotransmitters that initiate physiological events. Each receptor is coupled to distinct gustatory G-proteins and gustducin is the most common taste G-protein.

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Table 1:
Presence of chemosensory cells in endocrine cells of several regions of the gut as revealed by immunohistochemistry.

Cell type	Ligand	Chemosensory signaling element	Species	Localization	Ref
Brush cells					
		α-gustducin	rat, mouse	stomach, small intestine	[12-15, 17, 18]
		α-gustducin	mouse	colon	[13]
		no α-gustducin	mouse	esophagus	[15]
		α-transducin	rat	jejunum	[18]
		PLCβ2	rat	jejunum	[18]
		no PLCβ2	mouse	stomach, duodenum, colon	[13, 15]
		TRPM5	mouse	stomach, duodenum, colon	[13, 15]
	sweet/umami	TAS1R3	mouse	stomach, duodenum	[13, 16]
		No TAS1R3	mouse	colon	[13]
		No TAS1R3	rat	jejunum	[18]
	sweet	TAS1R2	rat	jejunum	[18]
	umami	TAS1R1	rat, mouse	duodenum	[13, 18]
	MCFA/LCFA	GPR120	mouse	stomach	[73]
Enteroendocrine cells					
Ghrelin (P, X/A-cells)		α-gustducin	mouse	stomach	[17]
		α-transducin	mouse	stomach	[17]
		no PLCβ2	human	stomach	[27]
		no TRPM5	human	stomach	[27]
		PLCβ2	mouse	stomach	[15]
	sweet/umami	TAS1R3	mouse	stomach, duodenum	[16]
	MCFA/LCFA	FFAR1 (only with desoctanoyl ghrelin)	mouse	stomach	[73]
		no FFAR1	mouse	duodenum	[73]
	MCFA/LCFA	GPR120	mouse	duodenum	[73]
		no GPR120	mouse	stomach	[73]
Gastrin (G-cells)		no PLCβ2	human, mouse	stomach	[60]
		PLCβ3	human, mouse	stomach	[60]
	sweet/umami	no T1R3	mouse	stomach	[59]
	aromatic AA	CaR	human, swine, mouse	stomach	[57-60]
	basic AA	GPRC6A	human, swine, mouse	stomach	[59, 60]
	peptone	GPR92	swine, mouse	stomach	[60]
	MCFA/LCFA	FFAR1	mouse	pylorus, duodenum	[72]
CCK (I-cells)	aromatic AA	CaR	mouse	duodenum	[61, 62]
	MCFA/LCFA	FFAR1	mouse	duodenum, pylorus	[72]
Somatostatin (D-cells)		PLCβ2	human, swine, mouse	stomach	[60]
	aromatic AA	CaR	human, swine, mouse	stomach	[60]

	basic AA	GPRC6A	human, swine, mouse	stomach	[59, 60]
	peptone	GPR92	mouse, swine	stomach	[60]
	MCFA/LCFA	no FFAR1	mouse	stomach	[72]
GLP-1 (L-cells)		α-gustducin	human	duodenum, colon	[23-25]
		α-gustducin	mouse	mid jejunum	[14]
		Gβ3	human	duodenum	[25]
		Gγ13	human	duodenum	[25]
		PLCβ2	human	duodenum	[25]
		TRPM5	human	duodenum	[25]
	sweet/umami	TAS1R3	human	duodenum, colon	[24, 25]
	MCFA/LCFA	FFAR1	mouse	pylorus, duodenum, ileum	[72]
	MCFA/LCFA	GPR120	human	colon	[80]
PYY (L-cells)		α-gustducin	human	colon	[23]
	MCFA/LCFA	FFAR1	mouse	pylorus, duodenum	[72]
	SCFA	GPR41	human	colon	[87]
	SCFA	GPR43	human, rat	colon	[86, 88]
		GPR43	rat	ileum	[88]
	oleoylethanolamide	GPR119	mouse	colon	[93]
GIP (K-cells)		α-gustducin	human, rat	duodenum	[25, 26]
	MCFA/LCFA	FFAR1	mouse	pylorus, duodenum	[72]
5-HT (EC-cells)		no α-gustducin	human	colon	[23]
		α-gustducin	mouse	mid jejunum	[14]
		no α-gustducin	mouse	stomach	[15]
		no α-gustducin	rat	duodenum	[12]
	MCFA/LCFA	FFAR1	mouse	pylorus, duodenum	[72]
	SCFA	no GPR41	human	colon	[87]
	SCFA	no GPR43	human, rat	colon	[86]
		no GPR43	rat	ileum	[86]

Legends to the figures

Figure 1: Simplified model of the pathways involved in chemosensory signalling in the gastrointestinal mucosa as reviewed in the current paper.

Nutrients (sweet, bitter, fat, amino acids) are sensed by different GPCRs as well as transporters in several cell types (endocrine cell, brush cell, enterocyte) of the epithelial lining that cross-regulate each others expression. The GPCRs induce via distinct G-proteins (e.g. gustducin) the release of second messengers that lead to the release of gut peptides which can communicate directly, via the blood stream, or indirectly, via the vagal nerve, with the hypothalamus, to control food intake.

AA: amino acid, AA-TS: amino acid transport systems. Note that transporters may also be expressed on endocrine cells.

Figure 2: Proposed model for the nutrient sensing mechanisms of the ghrelin cell.

Bitter tastants bind to taste receptors on the ghrelin cell or on the brush cells in the GI tract, coupling through α-gustducin to increase ghrelin secretion. This results in a short-term increase in food intake and accelerated gastric emptying, followed by a prolonged decrease in food intake, which correlates with a delay in gastric emptying. α-gustducin is involved in sensing of octanoic acid (MCFA) in the diet, necessary for the octanoylation of ghrelin, but the FFA receptor involved has not been elucidated yet. *In vitro* and *in vivo* studies suggest that GPR40 is not of major importance for lipid sensing of the ghrelin producing cells, but *in vitro* and *in vivo* studies with the GPR120 agonist, grifolic acid, point towards a direct or indirect role, mediated by the release of other gut hormones, of GPR120 in the lipid sensing cascade in ghrelin producing cells [17, 73].
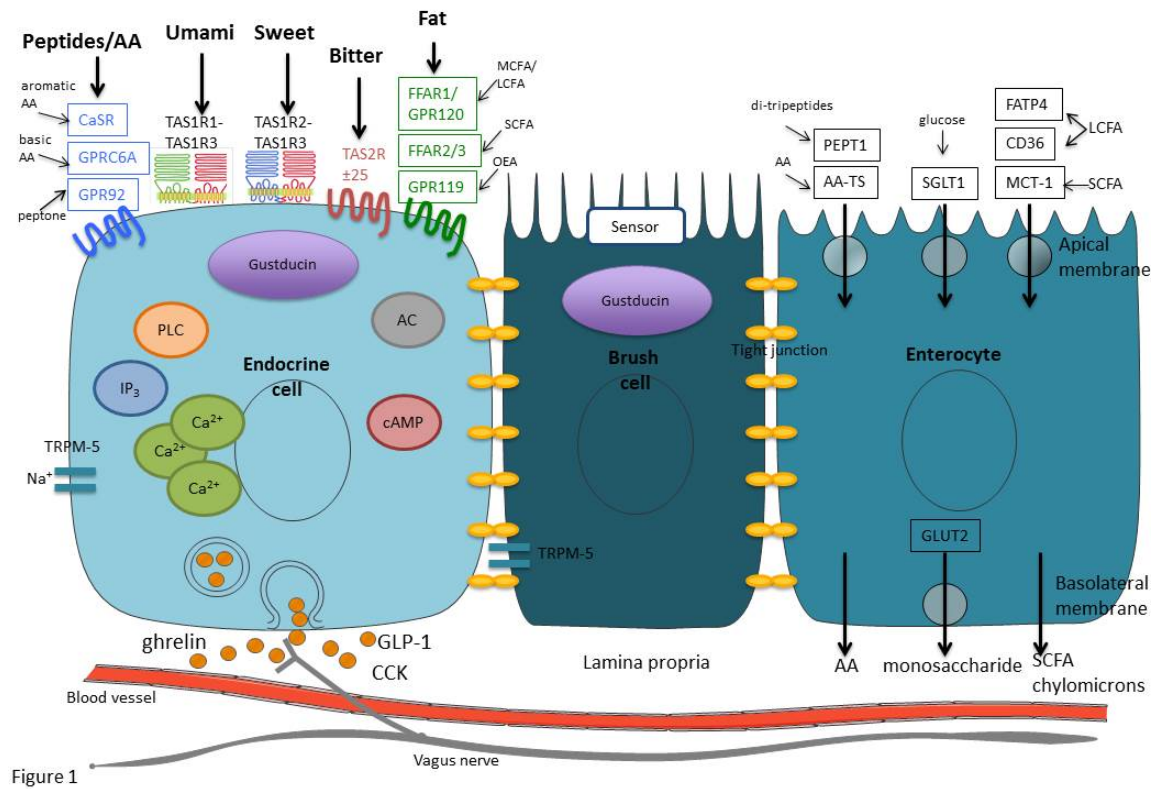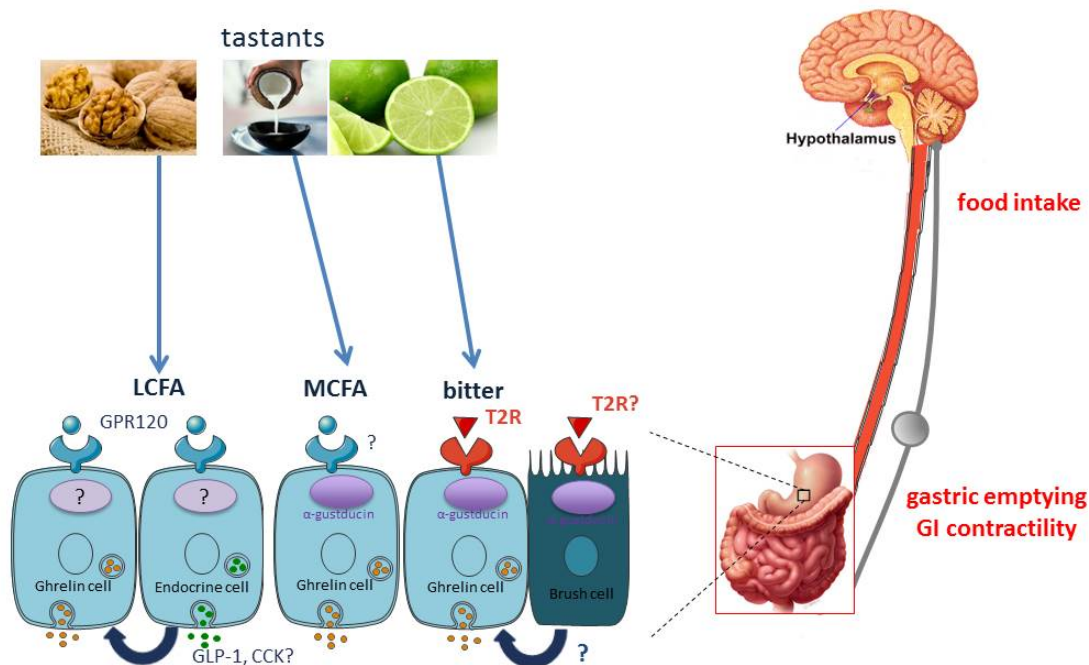
Figure 1

Figure 2