Review

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Nutrient sensing in the gut: new roads to therapeutics?

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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; they may thus be considered as new therapeutic targets.

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 water balance of the body. Umami taste is associated with protein-rich foods. Bitter taste is innately aversive and protects against the consumption of 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 are present on the tongue suggests that fat can be considered as the 6th 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, TRCs transmit the information via sensory afferent fibers to specific 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, whereas 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].

Glossary

Cholecystokinin (CCK): 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. In addition to 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 of 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, immediately after its release from the enteroendocrine L cells in the distal gut, is cleaved by dipeptidyl peptidase-4 to an antagonist (GLP-1 {9–36}). 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 being developed and are 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): 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 the transit of a meal through the gut to optimize nutrient digestion and absorption.

Taste receptors: seven transmembrane domain G protein-coupled receptors that are involved in the sensation of taste. The taste 1 receptor family (consisting of three subtypes) is involved in the sensation of sweet and umami, and 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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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]. In addition to α-gustducin, which affects cAMP and cGMP levels, a significant role in taste signaling is taken on by the βγ partners ($\beta_3\gamma_{13}$) of gustducin, which activate phospholipase $C_{\beta 2}$ ($PLC_{\beta 2}$) [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 the 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. 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, and other processes [9]. Luminal sensing is also critical for initiating an appropriate response, such as 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 domains 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

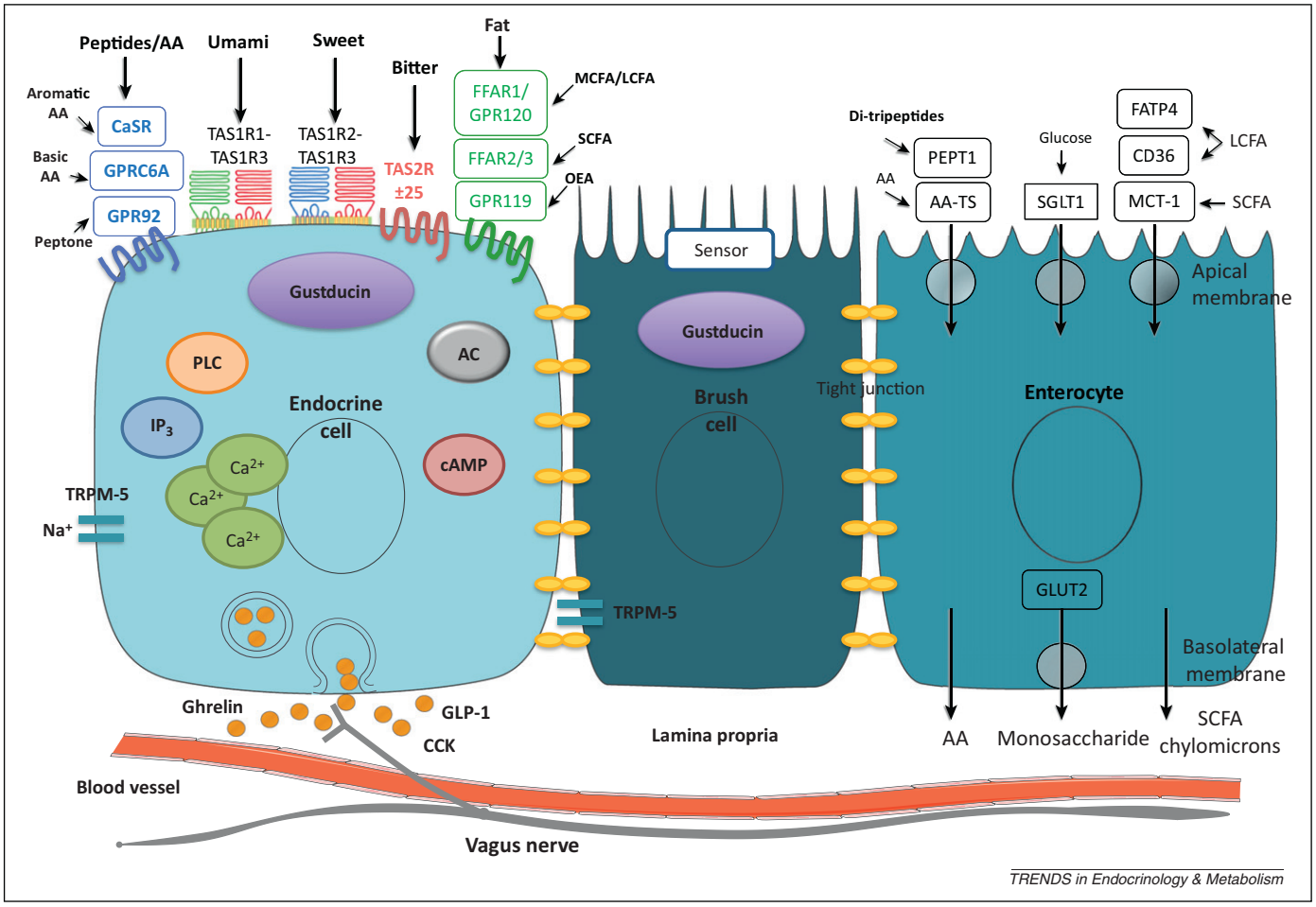

Figure 1. Simplified model of the pathways involved in chemosensory signaling in the gastrointestinal mucosa as reviewed in the current paper. Nutrients (sweet, bitter, fat, amino acids) are sensed by different G protein-coupled receptors (GPCRs) as well as transporters in several cell types (endocrine cell, brush cell, enterocyte) of the epithelial lining that crossregulate 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 bloodstream, 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.