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Peptide regulators of peripheral taste function

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Abstract

The peripheral sensory organ of the gustatory system, the taste bud, contains a heterogeneous collection of sensory cells. These taste cells can differ in the stimuli to which they respond and the receptors and other signaling molecules they employ to transduce and encode gustatory stimuli. This molecular diversity extends to the expression of a varied repertoire of bioactive peptides that appear to play important functional roles in signaling taste information between the taste cells and afferent sensory nerves and/or in processing sensory signals within the taste bud itself. Here, we review studies that examine the expression of bioactive peptides in the taste bud and the impact of those peptides on taste functions. Many of these peptides produced in taste buds are known to affect appetite, satiety or metabolism through their actions in the brain, pancreas and other organs, suggesting a functional link between the gustatory system and the neural and endocrine systems that regulate feeding and nutrient utilization.

Keywords

gustatory; sweet; neuropeptide; glucagon; glucagon-like peptide-1; cholecystokinin

1. Introduction

Sensory perceptions are not exact representations of the environment. Rather, these perceptions result from several layers of neural processing that occur after a stimulus is detected by sensory receptors. In this way, the recognition of specific sensory stimuli can be understood in the context of other sensory information as well as the animal's experience, motivation, and physiological state. While the central nervous system plays a fundamental role in sensory processing, the peripheral sensory organ can also critically shape the neural signals that are sent to the brain. The visual [1–3], olfactory [4–6], nociceptive [7], auditory [8, 9], vestibular [10] and somatosensory [11] systems all process sensory information to varying degrees at the level of the sensory organ. There is also growing evidence indicating

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that taste information undergoes significant processing within the gustatory sensory organ, the taste bud, as well as between the taste bud and the cranial nerves that carry gustatory information to the central nervous system. Recent reviews have done an excellent job of describing the roles of classical and non-classical small molecule neurotransmitters such as serotonin and adenosine triphosphate (ATP) in shaping peripheral taste responses [12, 13]. Here, we will focus on the emerging understanding of the role that peptide-mediated signaling may play in shaping gustatory responses in the taste bud.

Cells of the mammalian taste bud express a number of diverse peptide receptors and often their cognate ligands. All of these peptides have important roles outside the gustatory system, where they often act on nervous or endocrine tissues to regulate physiological responses. However, there is now an emerging view that these peptides, whether produced in the taste bud or in distant tissues, are impacting peripheral taste responsiveness through autocrine, paracrine and even endocrine signaling. Below, we discuss several peptides that are produced by taste bud cells as well as the evidence supporting roles for these peptides in regulating peripheral gustatory function.

2. The taste bud

Taste buds are collections of gustatory sensory cells, supporting cells and progenitor cells, and can be found on the dorsal surface of the tongue (on fungiform, foliate or circumvallate papillae) or on the soft palate [12, 13]. Taste cells are also found in the oropharynx. Taste cells can be differentiated based on morphology and ultrastructure, the expression of specific molecules, or their responses to taste stimuli that elicit distinct perceptual qualities (i.e., sweet, umami, bitter, sour or salty). Although these various criteria correspond imperfectly and may vary somewhat between species, certain useful generalizations for categorizing taste bud cells can still be made.

Taste cells fall into four morphological subtypes: Types I, II, III and IV [13]. Type I cells are thought to play a supporting, glial-like role. For example, they express proteins involved in the clearance or degradation of neurotransmitters, such as the ecto-nucleoside triphosphate diphosphohydrolase NTPDase2 [14]. However, the Type I cells may also include cells that mediate the salty taste of sodium chloride [15–17]. Non-overlapping subsets of Type II cells express receptors for sweet, bitter and umami taste and mediate the detection of those stimuli [18, 19]. All Type II cells appear to express the signaling molecules phospholipase Cβ 2 (PLCβ 2) and transient receptor potential channel M5 (TRPM5); only a subset express the G protein subunit α-gustducin [12]. Type II taste cells do not form traditional synapses with afferent nerve fibers. Type III cells, by contrast, do exhibit stereotypical presynaptic features including synaptic vesicles and vesicle fusion machinery such as SNAP-25 (e.g., [20, 21]). At least some Type III cells are sensors for sour stimuli (e.g., [22, 23]). Type IV cells are basal cells and are thought to contain precursor populations that can differentiate into other taste bud cell types [24].

Taste buds use both classical and non-classical small molecule transmitters to signal between taste cells and/or between taste cells and intragemmal nerve fibers. These molecules and their roles in taste have been reviewed in detail elsewhere [13], but a brief discussion is warranted here. As mentioned above, Type II cells do not exhibit typical synapses. In response to taste stimulation, these cells release ATP through hemichannels [25–28] that can then activate purinergic receptors (P2X2 and P2X3) present on the cranial nerve fibers innervating each taste bud [29, 30]. These cells also release acetylcholine [31, 32]. By contrast, type III taste cells release serotonin, norepinephrine and γ-aminobutyric acid (GABA) in response to gustatory stimulation [33–39]. While ATP appears to be the principal neurotransmitter linking taste cells to afferent nerves [25], these other transmitters

likely play important roles in modulating taste cell functions through autocrine and paracrine signaling and thus may help to shape the output of the taste bud [13].

In addition to these “classic” neurotransmitters, taste cells also express a large number of peptides that could act as neurotransmitters and/or neurohormones. The growing list includes glucagon [40, 41], glucagon-like peptide-1 (GLP-1) [40, 42], cholecystokinin (CCK) [43, 44], neuropeptide Y (NPY) [45], peptide tyrosine tyrosine (PYY) [46], vasoactive intestinal peptide (VIP) [43, 47, 48], ghrelin [49], and galanin [50]. In addition, cognate receptors for these peptides are expressed either in taste cells or on the intragemmal fibers of afferent taste nerves.

The presence of several neuropeptides and their receptors in taste buds suggest a role in the processing of taste information at the level of the taste bud. As with many of the classic neurotransmitters detailed above, it has been suggested that peptide-mediated autocrine and paracrine signaling may mediate cell-to-cell communication within the taste bud [51]. Some peptides may also act as endocrine signals to the brain or peripheral organs, just as peptide receptors in taste buds may respond to circulating peptides produced in the gut or other tissues. Such endocrine functions could allow for modulation of taste responses in the context of an animal’s metabolic state [52–61] or could prime the organism for the processing or disposal of ingested nutrients or toxins.

3. Peptides expressed in the taste bud

3.1 Glucagon-like peptide 1

Glucagon-like peptide 1 (GLP-1) is a 30-amino acid peptide hormone produced upon the cleavage of the prohormone proglucagon by the proprotein convertase PC1/3 (other peptides, including GLP-2 and glucagon, are also processed from proglucagon) [62]. GLP-1 is secreted from intestinal enteroendocrine L cells after meal ingestion [62]. Fats and sugars are both potent stimulators of GLP-1 secretion from the gut [63]. A major role of GLP-1 in the body is to regulate glucose homeostasis by stimulating insulin secretion (i.e., to act as an incretin hormone) and by inhibiting glucagon secretion from the endocrine pancreas [64]. GLP-1 also inhibits gastrointestinal motility and secretion as well as regulating appetite and food intake via actions in the hypothalamus. Thus, GLP-1 acts as part of the “ileal brake” to slow digestion and reduce ingestion [65]. Decreased secretion of GLP-1 may contribute to the development of obesity, and exaggerated secretion may be responsible for postprandial reactive hypoglycemia [62]. GLP-1 is rapidly inactivated in the bloodstream by the enzyme dipeptidyl peptidase IV (DPP-4) [62], raising the possibility that the actions of GLP-1 are mediated, at least in part, by the stimulation of nearby sensory neurons in the intestine and the liver that express the GLP-1 receptor (GLP-1R) [66].

GLP-1 is expressed by a subset of taste cells in mouse [40], rat [40, 42] and macaque [40]. The GLP-1-expressing taste cell population in the mouse circumvallate taste buds is heterogeneous: approximately half of all the GLP-1-expressing cells are also α-gustducin and T1R3 immunopositive, while the rest are serotonergic [40]. Thus, GLP-1 is found in both Type II and Type III taste cells. GLP-1 is co-expressed with PC1/3 [40], indicating that taste cells produce GLP-1 autonomously rather than accumulating GLP-1 from the bloodstream or adjacent tissues. These taste cells produce an active form of GLP-1, as extracts of lingual epithelium can stimulate heterologous cells expressing the GLP-1R [40].

GLP-1Rs are not found on taste cells, but rather are located on PGP 9.5-positive intragemmal nerve fibers innervating the taste bud [40]. The proximity of GLP-1 and its cognate receptor suggests that taste cell-derived GLP-1 is primarily a paracrine factor, although the peptide could also enter the circulation. In blood and intestine, GLP-1 is

quickly inactivated by DPP-IV, but both immunohistochemical and RT-PCR analysis of circumvallate taste buds shows that they contain little to no DPP-IV [40]. Thus, the half-life of GLP-1 in taste buds should be high, ensuring sufficient concentrations within the taste bud to stimulate the nearby GLP-1R.

The presence of GLP-1 and its receptor in taste buds suggests a role in shaping taste responses. This appears to be the case. GLP-1R knockout mice [67] display a significantly reduced responsiveness in brief access behavioral taste tests to both natural (sucrose) and artificial (sucralose) sweeteners as compared to wildtype controls [40]. No significant differences in taste responses were seen for bitter, salt, or sour stimuli [40], but the knockout mice do show a surprising increase in taste responsiveness to the umami stimulus monosodium glutamate [68]. A similar decrement in taste behavioral responses to sucrose was seen using the same mouse line and a different short term lick assay [69] (although rats receiving systemic injections of the GLP-1R antagonist exendin-3(9–39) do not exhibit a decrease in sucrose consummatory behavior [70]). Together, these behavioral data support a role for GLP-1 in the modulation of peripheral responses to appetitive taste stimuli. Such a role is further supported by recent experiments showing that stimulation of circumvallate taste buds with sweet or umami stimuli (Geraedts and Munger, unpublished observations) or with long chain fatty acids [69] can elicit the secretion of GLP-1. Additional experiments, such as ones examining the physiological responses of taste cells or taste nerve afferents to alterations in GLP-1 signaling, could help refine the function of GLP-1 and its receptor in the peripheral gustatory system.

3.2 Glucagon

Glucagon is a 29 amino acid peptide that is proteolytically cleaved from proglucagon by the proprotein convertase PC2. It is primarily produced in pancreatic β cells and acts to increase blood glucose concentration by stimulating glycogen breakdown and activating gluconeogenesis within the liver [71]. In addition, glucagon stimulates insulin secretion from pancreatic β cells [72] and inhibits further glucagon secretion from α cells[73, 74], thus helping the organism to avoid hyperglycemia. Glucagon signals through a G protein-coupled glucagon receptor (GlucR), which is found in liver, kidney and several other tissues [75].

Glucagon is produced in subsets mouse taste cells in the circumvallate, foliate, and fungiform papillae, where it is co-expressed with the GlucR [40, 41]. Glucagon/GluR-positive cells also express PC2 and its obligatory co-factor 7B2, indicating that glucagon is produced in taste cells [40, 41]. These signaling components are almost wholly restricted to Type II taste cells, with 95% of the immunopositive cells expressing the enzyme PLCβ 2 and 93% expressing the sweet and umami taste receptor subunit T1R3 [41]. However, only about half of the cells expressing glucagon and the GlucR also express α-gustducin. Together with glucagon's almost complete exclusion from serotonergic Type III cells, it is clear that glucagon and its fellow proglucagon product GLP-1 are found in partially overlapping cell populations within the taste bud. However, systematic expression analyses of these two peptides are required to establish the extent of overlap.

Disruption of glucagon signaling by either genetic or pharmacological manipulations results in decreased sweet taste responsiveness in behavioral tests [41]. Mice that lack the PC2 chaperone 7B2 (i.e., *Scg5*$^{-/-}$ mice), and thus cannot process glucagon from its precursor, are less responsive to sucrose in brief access taste tests than are their littermate controls. These mice show no decrements in their responses to salty, sour or bitter stimuli. The contribution of glucagon signaling to taste function appears to be at the level of the taste bud, as wildtype mice receiving a potent, membrane-permeable GlucR antagonist in the taste solution exhibited a similar taste behavior phenotype. These results indicate that glucagon signaling

in the taste bud, like GLP-1 signaling, acts to enhance or maintain sweet taste responsiveness. However, in contrast to GLP-1, which targets GLP-1 receptors on closely apposed afferent nerve fibers [40], glucagon appears to function as an autocrine signal for taste cells. Furthermore, basal glucagon secretion from circumvallate papillae is inhibited by appetitive stimuli (Geraedts and Munger, unpublished observations).

3.3 Cholecystokinin

Cholecystokinin (CCK) is cleaved from the proprotein, preprocholecystokinin. It is closely related to another peptide hormone, gastrin. The length of CCK can vary depending on posttranslational processing, but all variants contain the same eight residues at the carboxy end. In the GI tract, CCK is produced by enteroendocrine I cells, a cell population that is largely restricted to the duodenum [76]. CCK promotes digestion by regulating the production of bile and pancreatic enzymes, and satiety through actions in the hypothalamus. The two CCK receptor subtypes, CCK_A and CCK_B, vary in sequence, anatomical distribution and ligand selectivity (CCK_B, but not CCK_A, responds to gastrin as well as CCK) [77].

In the gustatory system, CCK expression was first described in rat taste buds [44]. Immunoreactivity for the sulfated CCK octapeptide was found in taste buds of foliate and circumvallate papillae, palate, and the nasoincisor ducts, while expression was confirmed by RT-PCR[44]. Like GLP-1 and glucagon, CCK is confined to subpopulations of taste cells. In taste buds of the foliate and circumvallate papillae approximately half of CCK-expressing taste cells are immunopositive for α-gustducin, but only 15% coexpress the sweet taste receptor subunit T1R2 [43]. These findings suggested that CCK impacts bitter and/or sweet taste responses.

The physiological roles of CCK in taste have been assessed in both isolated taste cells and in behaving animals. Colocalization of CCK and the CCK_A receptor suggests that the peptide acts largely as an autocrine signal within the taste bud [44]. Patch clamp electrophysiological recordings from acutely isolated circumvallate and foliate taste cells showed that focal application of exogenous CCK inhibits both delayed rectifier and inward rectifier potassium currents in a subset of cells [44]. These observations suggest that one role of CCK signaling could be to modulate the excitability of taste cells or to prolong their depolarization after stimulation. CCK also increases intracellular calcium levels in isolated taste cells [44], likely through the CCK_A-mediated activation of a phosphoinositide signaling pathway.

The consequences of CCK signaling on taste coding and taste behavior remain unclear. Because of the significant overlap of CCK and α-gustducin in the taste bud, it was hypothesized that CCK signaling plays a key role in bitter taste signaling [44, 51]. However, behavioral experiments suggest a role in responses to appetitive taste stimuli. Otsuka Long-Evans Tokushima fatty (OLETF) rats, which lack a functional CCK_A receptor, exhibit enhanced behavioral (i.e., lick) responses to sweet substances and MSG as compared to lean Long-Evans Tokushima Otsuka (LETO) controls [78]. Of course, the disruption of CCK signaling is not restricted to gustatory tissues in these rats. Elucidation of the role of CCK signaling in the taste bud awaits physiological and behavioral studies that can resolve the local global contributions of CCK to taste responsiveness.

3.4 Vasoactive intestinal peptide (VIP)

Vasoactive intestinal peptide (VIP) is a 28-amino acid peptide originally isolated from porcine ileum [79]. VIP is cleaved from preprovasoactive intestinal polypeptide. Although its functions were at first thought to be restricted to the gut, VIP is now well established as a

neurohormone with actions in both the central and peripheral nervous system [80]. As a transmitter in autonomic nerves, VIP plays important roles in the control of smooth muscle tone, blood flow, and secretion in the digestive, respiratory and urogenital tracts. For example, in the digestive system VIP can induce smooth muscle relaxation in the lower esophageal sphincter, stomach and gallbladder; stimulate water secretion into pancreatic juice and bile; and cause inhibition of gastric acid secretion and absorption from the intestinal lumen [81]. The biological effects of VIP are mediated by either of two G protein-coupled receptors: VIP/PACAP (pituitary adenylate cyclase activating peptide) receptor type 1 (VPAC1) and VIP/PACAP receptor type 2 (VPAC2) [82].

Rat foliate and circumvallate taste buds contain large numbers of VIP-immunoreactive cells [47]. VIP immunoreactivity has also been reported in a subset of human circumvallate taste cells [83]. In the rat, approximately 60% of VIP-immunoreactive taste cells express α-gustducin, while only 19% express the sweet taste receptor subunit T1R2 [43]. The localization of both VPAC1 and VPAC2 receptors to a subset of PLCβ 2-immunopositive taste cells [48] suggests that VIP signaling is local to the taste bud, but it is unknown whether VIP acts as an autocrine or paracrine factor. The VIP- and CCK-positive cell subpopulations are largely overlapping, with three-fourths of VIP-expressing cells also expressing the other peptide [45].

There has only been a single study addressing VIP's role in taste responses. In that study, VIP knockout mice exhibited subtle changes in brief access taste responses to sucrose (increased EC_{50}), denatonium benzoate (decreased EC_{50}) and citric acid (increased EC_{50}) [48]. It is unclear why sweet and bitter responses were differentially altered, or why sour responses would be expected to change when VPAC1 and VPAC2 are excluded from sour-sensing (Type III) cells. Furthermore, the taste buds of VIP knockout mice show alterations in the expression other molecules (GLP-1, leptin receptors) that could impact these taste responses. At any rate, a full understanding of the mechanisms by which VIP signaling in the taste bud impacts gustatory function awaits further study.

2.5 Neuropeptide Y (NPY) and Peptide YY (PYY)

The neuropeptide Y (NPY) family of peptides and their cognate receptors has been strongly implicated in the regulation of energy homeostasis [84–86]. The NPY family consists of three 36-amino acid peptides: NPY, peptide tyrosine tyrosine (PYY), and pancreatic polypeptide (PP), all of which influence energy balance via their unique interactions with G-protein-coupled Y receptors (Y1, Y2, Y4, Y5 and y6, the last of which is expressed in mice but not in humans [86]).

2.5.1 NPY—NPY is a 36 amino acid peptide [87] and is one of the earliest-recognized and most potent orexigenic neuropeptides acting in the hypothalamus. NPY has been implicated in the stimulation of food intake as well as locomotion, learning and memory, anxiety, epilepsy, circadian rhythm, and cardiovascular function. These differences in NPY actions result from the activation of several receptor isoforms that vary in their distribution and ligand selectivity. For example, Y1 and Y5 receptors have known roles in the stimulation of feeding while Y2 and Y4 are important in appetite inhibition [88–90].

NPY-positive taste cells are found in the nasoincisor ducts, and in the foliate, circumvallate, and fungiform papillae [45]. NPY co-localizes almost completely with both CCK and VIP, indicating that the gustatory epithelium contains a subpopulation of taste cells that express all three peptides. The expression of Y receptors in taste tissue has been assessed by immunohistochemistry, *in situ* hybridization and RT-PCR. Y1, Y2, Y4 and Y5 receptors have all been found in subpopulations of mouse taste cells [91]; Y1 expression has also been

reported in rat taste cells [51]. In the mouse CV, the Y4 receptor is also expressed in NCAM-positive nerve fibers innervating taste cells [91].

Little is known about the function of NPY in taste buds. Exogenous NPY does enhance inwardly rectifying potassium currents in isolated taste cells, suggesting a role in modulating taste cell excitability [45]. Pharmacological manipulations indicate that this effect is largely dependent on the Y1 receptor [45]. Based on its role in other tissues, including the olfactory system [92], NPY may also serve as a proliferative factor in the taste bud. The existence of gene-targeted lines carrying disruption of NPY or the Y receptors will be invaluable tools for dissecting the role of NPY in peripheral taste function.

2.5.2 PYY—The function of PYY remains unclear [84]. However, its distribution suggests a role in central regulation of energy metabolism. PYY is primarily secreted from endocrine cells of the pancreas, small intestine and colon. The peptide is found in two forms: the full length $PYY_{1–36}$ and the truncated form $PYY_{3–36}$. Cleavage of $PYY_{1–36}$ by DPP-IV yields the long C-terminal fragment [93] that is the most common form found in circulation. $PYY_{1–36}$ is relatively non-selective for all Y receptor subtypes whereas $PYY_{3–36}$ is highly selective for the Y2 receptor [86]. Both peptide forms suppress appetite and food intake and delay gastric emptying [84–86].

As described above, taste cells express four different Y receptor isoforms, while the Y4 variant is also expressed on afferent nerve fibers innervating the taste buds [91]. PYY immunoreactivity has also been found in a subpopulation of mouse taste cells (Dotson, unpublished data) as well as in mouse and human saliva [46]. As DPP-IV is not expressed in taste buds [40, 94], it is likely that $PYY_{1–36}$ is the primary form found in this tissue. $PYY_{1–36}$ is relatively non-selective for different Y receptors; thus, it is reasonable to expect that PYY peptide produced in the taste bud could exert effects on both taste cells and afferent nerves. By contrast, saliva contains $PYY_{3–36}$ [46], which preferentially acts via Y2 receptors and may have more targeted effects on subsets of taste cells.

2.6 Ghrelin

Ghrelin is produced primarily by endocrine cells in the stomach [95, 96]. It is the only potent orexigenic peptide found in circulation. Ghrelin has many known functions including a role in metabolic, behavioral, cardiovascular, reproductive and immunologic processes [97]. However, ghrelin is associated mostly with its stimulation of appetite and growth hormone production. Ghrelin signals through the G protein-coupled growth hormone secretagogue receptor (GHSR). The active variant of this receptor, known as GHSR1a, is expressed in numerous tissues including the hypothalamus, pituitary gland and several peripheral organs (e.g., heart, lung, liver, pancreas, and kidney) [97]. This broad expression suggests multiple functions for ghrelin both within and outside the nervous system.

Taste buds express several components of a ghrelin signaling mechanism, as assessed by a combination of immunohistochemistry and quantitative real-time PCR [49]. Ghrelin, its precursor preproghrelin and the processing enzyme PC1/3 are coexpressed in a subpopulation (~13%) of circumvallate taste bud cells [49]. Ghrelin immunoreactivity is not restricted to a single cell type in mouse taste tissue, but is found in Type I, II, III and IV cells. However, the acetylating enzyme ghrelin-O-acyltransferase (GOAT), which is required for ghrelin activation, is restricted to a subset of ghrelin-expressing cells [49]. Thus, it appears that activated ghrelin is produced in only those taste cells that express GOAT, although it is unclear which types of taste cells express this enzyme. By contrast, GHSR is more broadly expressed, with GHSR-immunoreactivity largely coincident with that for ghrelin itself [49].

There has only been a single behavioral study examining the role of ghrelin signaling in taste responsiveness. In this brief-access study, GHSR null mice exhibit slightly elevated EC_{50}s for NaCl and citric acid (but not sweet or bitter stimuli) in brief access taste tests as compared to wildtype controls [49]. However, it is important to know whether mice lacking other components of ghrelin signaling, such as GOAT or ghrelin itself, exhibit an equivalent phenotype.

2.7 Galanin

Galanin is located predominantly in the central nervous system and gastrointestinal tract [98–100]. Within the central nervous system, galanin is most heavily expressed in the hypothalamus; within the gastrointestinal tract it is most abundant in the duodenum [101]. The physiological roles of galanin remain poorly characterized, but the peptide has been linked to such diverse functions as the modulation of food intake, gut secretion and gut motility and to diseases such as Alzheimer's and epilepsy [102, 103]. Galanin may also have neurotrophic effects. There are three G protein-coupled galanin receptors, GALR1, GALR2 and GALR3 [100, 104, 105]. These receptors are differentially distributed in the central nervous system and are also found in the pancreas.

Galanin is expressed in taste cells of the circumvallate papillae [50], as assessed by RT-PCR, immunohistochemistry and *in situ* hybridization. Galanin-immunoreactive cells also express either NCAM, PLCβ2 and/or α-gustducin. Most, if not all, PLCβ2- and α-gustducin-immunopositive taste cells were found to express galanin. GalR2 receptor message, but not that of GalR1 or GalR3, was detected by RT-PCR in cDNA isolated from CV papillae and by *in situ* hybridization in CV taste buds, suggesting that this receptor isoform is the primary target of galanin in taste tissue. No studies have been reported that assess the role of galanin in taste. However, one possibility is that galanin serves a developmental role in taste buds analogous to the neurotrophic role it plays for some sensory neurons [50, 106].

3. Summary

It is now clear that taste cells express a number of bioactive peptides. Furthermore, there is growing evidence that these peptides can impact taste function at the level of the gustatory periphery. However, we only have a cursory understanding of the conditions under which these peptides are released, the contributions they make to sensory coding, and the mechanisms by which they exert their effects. For example, is peptide signaling in taste cells linked to activation of the cells by tastants, by endocrine signals, or by other factors? How do taste cells transduce peptide signals and how does this transduction influence tastant transduction and/or taste cell excitability? What aspects of taste functioning (e.g., sensory/discriminative, affective/motivational) are influenced by individual peptides? How do the various peptides and small molecule autocrine/paracrine signals present in the taste bud work together to influence the output of individual taste cells and of the taste bud as a whole? All of these questions have important implications for taste coding.

It has long been hypothesized that peripheral taste functions are modulated in the context of an animal's metabolic state [40, 41, 52–61]. In such a model, circulating gastrointestinal peptides could impact taste bud physiology through actions on locally expressed receptors. Indeed, it has been postulated that alterations in the levels of circulating hormones mediate the changes in taste perception observed after gastric bypass surgery [55, 107, 108]. Additionally, the adipose tissue-derived hormone leptin has been shown in behavioral and physiological assays to impact sweet taste responses through the activation of functional leptin receptors present in the taste bud [59–61]. Taste buds (specifically, Type I cells) also express the oxytocin receptor but not oxytocin [109]; the effects of oxytocin on taste

functions are unclear. Because endocrine signaling in the oral cavity is likely to influence food intake and satiety, it is critical to understand how major hormones influence taste perception and food intake. This fact has raised a fundamental challenge to the field to understand how these peripheral hormones affect taste function and ingestive behavior. Given the worldwide rising incidence of diabetes, obesity and related metabolic disorders, addressing our dearth of knowledge regarding the hormonal modulation of chemosensory perception and how disruption of hormonal signaling in the taste system can impact upon food intake and energy homeostasis seems warranted.

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Abbreviations

ATP	adenosine triphosphate
PLCβ 2	phospholipase Cβ 2
TRPM5	transient receptor potential channel M5
SNAP25	synaptosomal-associated protein 25
P2XR2	purinergic receptor X2, ligand-gated ion channel, 2
P2XR3 purinergic receptor X2	ligand-gated ion channel, 3
GABA	γ-aminobutyric acid
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
DPP-4	dipeptidyl peptidase 4
CCK	cholecystokinin
PYY	peptide YY
NPY	neuropeptide Y
VIP	vasoactive intestinal peptide
PACAP	pituitary adenylyl cyclase-activating peptide
PC1/3	proprotein convertase 1/3
PC2	proprotein convertase 2
PGP9.5	protein gene product 9.5
GlucR	glucagon receptor
7B2	neuroendocrine protein 7B2
OLETF	Otsuka Long-Evans Tokushima Fatty rat
LETO	Long-Evans Tokushima Otsuka rat
RT-PCR	reverse transcription-polymerase chain reaction
GHSR	growth hormone secretagogue receptor
GOAT	ghrelin O-acyltransferase
GALR	galanin receptor

cDNA	complementary DNA
CV	circumvallate

References

1. Field GD, Chichilnisky EJ. Information processing in the primate retina: circuitry and coding. Annu Rev Neurosci. 2007; 30:1–30. [PubMed: 17335403]
2. Tranchina D, Gordon J, Shapley R, Toyoda J. Linear information processing in the retina: a study of horizontal cell responses. Proc Natl Acad Sci U S A. 1981; 78:6540–2. [PubMed: 6947242]
3. Schiller PH. Parallel information processing channels created in the retina. Proc Natl Acad Sci U S A. 2010; 107:17087–94. [PubMed: 20876118]
4. Leinwand SG, Chalasani SH. Olfactory networks: from sensation to perception. Curr Opin Genet Dev. 2011; 21:806–11. [PubMed: 21889328]
5. Savigner A, Duchamp-Viret P, Grosmaitre X, Chaput M, Garcia S, Ma M, et al. Modulation of spontaneous and odorant-evoked activity of rat olfactory sensory neurons by two anorectic peptides, insulin and leptin. J Neurophysiol. 2009; 101:2898–906. [PubMed: 19297511]
6. Hall RA. Autonomic modulation of olfactory signaling. Sci Signal. 2011; 4:pe1. [PubMed: 21224443]
7. Levine JD, Fields HL, Basbaum AI. Peptides and the primary afferent nociceptor. J Neurosci. 1993; 13:2273–86. [PubMed: 8501507]
8. Kurt S, Sausbier M, Ruttiger L, Brandt N, Moeller CK, Kindler J, et al. Critical role for cochlear hair cell BK channels for coding the temporal structure and dynamic range of auditory information for central auditory processing. FASEB J. 2012; 26:3834–43. [PubMed: 22691916]
9. Meyer AC, Moser T. Structure and function of cochlear afferent innervation. Curr Opin Otolaryngol Head Neck Surg. 2010; 18:441–6. [PubMed: 20802334]
10. Ross MD, Donovan K. Gravity receptors: an ultrastructural basis for peripheral sensory processing. Physiologist. 1984; 27:S85–6. [PubMed: 11539018]
11. Davies SN. Evidence for peripheral, but not central modulation of trigeminal cold receptive cells in the rat. Brain Res. 1984; 301:299–305. [PubMed: 6733494]
12. Yarmolinsky DA, Zuker CS, Ryba NJ. Common sense about taste: from mammals to insects. Cell. 2009; 139:234–44. [PubMed: 19837029]
13. Chaudhari N, Roper SD. The cell biology of taste. J Cell Biol. 2010; 190:285–96. [PubMed: 20696704]
14. Bartel DL, Sullivan SL, Lavoie EG, Sevigny J, Finger TE. Nucleoside triphosphate diphosphohydrolase-2 is the ecto-ATPase of type I cells in taste buds. J Comp Neurol. 2006; 497:1–12. [PubMed: 16680780]
15. Yoshida R, Horio N, Murata Y, Yasumatsu K, Shigemura N, Ninomiya Y. NaCl responsive taste cells in the mouse fungiform taste buds. Neuroscience. 2009; 159:795–803. [PubMed: 19167465]
16. Vandenbeuch A, Clapp TR, Kinnamon SC. Amiloride-sensitive channels in type I fungiform taste cells in mouse. BMC Neurosci. 2008; 9:1. [PubMed: 18171468]
17. Chandrashekar J, Kuhn C, Oka Y, Yarmolinsky DA, Hummler E, Ryba NJ, et al. The cells and peripheral representation of sodium taste in mice. Nature. 2010; 464:297–301. [PubMed: 20107438]
18. Nelson G, Hoon MA, Chandrashekar J, Zhang Y, Ryba NJ, Zuker CS. Mammalian sweet taste receptors. Cell. 2001; 106:381–90. [PubMed: 11509186]
19. Adler E, Hoon MA, Mueller KL, Chandrashekar J, Ryba NJ, Zuker CS. A novel family of mammalian taste receptors. Cell. 2000; 100:693–702. [PubMed: 10761934]
20. DeFazio RA, Dvoryanchikov G, Maruyama Y, Kim JW, Pereira E, Roper SD, et al. Separate populations of receptor cells and presynaptic cells in mouse taste buds. J Neurosci. 2006; 26:3971–80. [PubMed: 16611813]

21. Clapp TR, Medler KF, Damak S, Margolskee RF, Kinnamon SC. Mouse taste cells with G protein-coupled taste receptors lack voltage-gated calcium channels and SNAP-25. BMC Biol. 2006; 4:7. [PubMed: 16573824]
22. Huang A, Chen X, Hoon M, Chandrashekar J, Guo W, Tränkner D, et al. The cells and logic for mammalian sour taste detection. Nature. 2006; 442:934–8. [PubMed: 16929298]
23. Kataoka S, Yang R, Ishimaru Y, Matsunami H, Sévigny J, Kinnamon J, et al. The candidate sour taste receptor, PKD2L1, is expressed by type III taste cells in the mouse. Chem Senses. 2008; 33:243–54. [PubMed: 18156604]
24. Sullivan JM, Borecki AA, Oleskevich S. Stem and progenitor cell compartments within adult mouse taste buds. Eur J Neurosci. 2010; 31:1549–60. [PubMed: 20525068]
25. Finger TE, Danilova V, Barrows J, Bartel DL, Vigers AJ, Stone L, et al. ATP signaling is crucial for communication from taste buds to gustatory nerves. Science. 2005; 310:1495–9. [PubMed: 16322458]
26. Huang YJ, Maruyama Y, Dvoryanchikov G, Pereira E, Chaudhari N, Roper SDCP. The role of pannexin 1 hemichannels in ATP release and cell-cell communication in mouse taste buds. Proc Natl Acad Sci U S A. 2007; 104:6436–41. [PubMed: 17389364]
27. Dando R, Roper SD. Cell-to-cell communication in intact taste buds through ATP signalling from pannexin 1 gap junction hemichannels. J Physiol. 2009; 587:5899–906. [PubMed: 19884319]
28. Romanov RA, Rogachevskaja OA, Bystrova MF, Jiang P, Margolskee RF, Kolesnikov SS. Afferent neurotransmission mediated by hemichannels in mammalian taste cells. EMBO J. 2007; 26:657–67. [PubMed: 17235286]
29. Bo X, Alavi A, Xiang Z, Oglesby I, Ford A, Burnstock G. Localization of ATP-gated P2X2 and P2X3 receptor immunoreactive nerves in rat taste buds. Neuroreport. 1999; 10:1107–11. [PubMed: 10321492]
30. Yang R, Montoya A, Bond A, Walton J, Kinnamon JC. Immunocytochemical Analysis of P2X2 in Rat Circumvallate Taste Buds. BMC Neurosci. 2012; 13:51. [PubMed: 22621423]
31. Dando R, Roper SD. Acetylcholine is released from taste cells, enhancing taste signalling. J Physiol. 2012; 590:3009–17. [PubMed: 22570381]
32. Ogura T. Acetylcholine increases intracellular Ca2+ in taste cells via activation of muscarinic receptors. J Neurophysiol. 2002; 87:2643–9. [PubMed: 12037167]
33. Dvoryanchikov G, Huang YA, Barro-Soria R, Chaudhari N, Roper SD. GABA, its receptors, and GABAergic inhibition in mouse taste buds. J Neurosci. 2011; 31:5782–91. [PubMed: 21490220]
34. Huang YA, Maruyama Y, Roper SD. Norepinephrine is coreleased with serotonin in mouse taste buds. J Neurosci. 2008; 28:13088–93. [PubMed: 19052199]
35. Huang YA, Maruyama Y, Stimac R, Roper SD. Presynaptic (Type III) cells in mouse taste buds sense sour (acid) taste. J Physiol. 2008; 586:2903–12. [PubMed: 18420705]
36. Huang YA, Dando R, Roper SD. Autocrine and paracrine roles for ATP and serotonin in mouse taste buds. J Neurosci. 2009; 29:13909–18. [PubMed: 19890001]
37. Huang YA, Pereira E, Roper SD. Acid stimulation (sour taste) elicits GABA and serotonin release from mouse taste cells. PLoS One. 2011; 6:e25471. [PubMed: 22028776]
38. Obata H, Shimada K, Sakai N, Saito N. GABAergic neurotransmission in rat taste buds: immunocytochemical study for GABA and GABA transporter subtypes. Brain Res Mol Brain Res. 1997; 49:29–36. [PubMed: 9387860]
39. Cao Y, Zhao FL, Kolli T, Hivley R, Herness S. GABA expression in the mammalian taste bud functions as a route of inhibitory cell-to-cell communication. Proc Natl Acad Sci U S A. 2009; 106:4006–11. [PubMed: 19223578]
40. Shin YK, Martin B, Golden E, Dotson CD, Maudsley S, Kim W, et al. Modulation of taste sensitivity by GLP-1 signaling. J Neurochem. 2008; 106:455–63. [PubMed: 18397368]
41. Elson AE, Dotson CD, Egan JM, Munger SD. Glucagon signaling modulates sweet taste responsiveness. FASEB J. 2010; 24:3960–9. [PubMed: 20547661]
42. Feng XH, Liu XM, Zhou LH, Wang J, Liu GD. Expression of glucagon-like peptide-1 in the taste buds of rat circumvallate papillae. Acta Histochem. 2008; 110:151–4. [PubMed: 18054375]

43. Shen T, Kaya N, Zhao FL, Lu SG, Cao Y, Herness S. Co-expression patterns of the neuropeptides vasoactive intestinal peptide and cholecystokinin with the transduction molecules alpha-gustducin and T1R2 in rat taste receptor cells. Neuroscience. 2005; 130:229–38. [PubMed: 15561439]
44. Herness S, Zhao FL, Lu SG, Kaya N, Shen T. Expression and physiological actions of cholecystokinin in rat taste receptor cells. J Neurosci. 2002; 22:10018–29. [PubMed: 12427859]
45. Zhao FL, Shen T, Kaya N, Lu SG, Cao Y, Herness SC. Expression, physiological action, and coexpression patterns of neuropeptide Y in rat taste-bud cells. Proc Natl Acad Sci U S A. 2005; 102:11100–5. [PubMed: 16040808]
46. Acosta A, Hurtado MD, Gorbatyuk O, La Sala M, Duncan D, Aslanidi G, et al. Salivary PYY: a putative bypass to satiety. PLoS One. 2011; 6:e26137. [PubMed: 22028819]
47. Herness MS. Vasoactive intestinal peptide-like immunoreactivity in rodent taste cells. Neuroscience. 1989; 33:411–9. [PubMed: 2622534]
48. Martin B, Shin YK, White CM, Ji S, Kim W, Carlson OD, et al. Vasoactive intestinal peptide-null mice demonstrate enhanced sweet taste preference, dysglycemia, and reduced taste bud leptin receptor expression. Diabetes. 2010; 59:1143–52. [PubMed: 20150284]
49. Shin YK, Martin B, Kim W, White CM, Ji S, Sun Y, et al. Ghrelin is produced in taste cells and ghrelin receptor null mice show reduced taste responsivity to salty (NaCl) and sour (citric acid) tastants. PLoS One. 2010; 5:e12729. [PubMed: 20856820]
50. Seta Y, Kataoka S, Toyono T, Toyoshima K. Expression of galanin and the galanin receptor in rat taste buds. Arch Histol Cytol. 2006; 69:273–80. [PubMed: 17287581]
51. Herness S, Zhao FL. The neuropeptides CCK and NPY and the changing view of cell-to-cell communication in the taste bud. Physiol Behav. 2009; 97:581–91. [PubMed: 19332083]
52. Shin AC, Townsend RL, Patterson LM, Berthoud HR. “Liking” and “wanting” of sweet and oily food stimuli as affected by high-fat diet-induced obesity, weight loss, leptin, and genetic predisposition. Am J Physiol Regul Integr Comp Physiol. 2011; 301:R1267–80. [PubMed: 21849633]
53. Le Roux CW, Bueter M, Theis N, Werling M, Ashrafian H, Lowenstein C, et al. Gastric bypass reduces fat intake and preference. Am J Physiol Regul Integr Comp Physiol. 2011
54. Tichansky DS, Glatt AR, Madan AK, Harper J, Tokita K, Boughter JD. Decrease in sweet taste in rats after gastric bypass surgery. Surg Endosc. 2011; 25:1176–81. [PubMed: 20844896]
55. Hajnal A, Kovacs P, Ahmed T, Meirelles K, Lynch CJ, Cooney RN. Gastric bypass surgery alters behavioral and neural taste functions for sweet taste in obese rats. Am J Physiol Gastrointest Liver Physiol. 2010; 299:G967–79. [PubMed: 20634436]
56. Olbers T, Bjorkman S, Lindroos A, Maleckas A, Lonn L, Sjostrom L, et al. Body composition, dietary intake, and energy expenditure after laparoscopic Roux-en-Y gastric bypass and laparoscopic vertical banded gastroplasty: a randomized clinical trial. Ann Surg. 2006; 244:715–22. [PubMed: 17060764]
57. Chen K, Yan J, Suo Y, Li J, Wang Q, Lv B. Nutritional status alters saccharin intake and sweet receptor mRNA expression in rat taste buds. Brain Res. 2010
58. Umabiki M, Tsuzaki K, Kotani K, Nagai N, Sano Y, Matsuoka Y, et al. The improvement of sweet taste sensitivity with decrease in serum leptin levels during weight loss in obese females. Tohoku J Exp Med. 2010; 220:267–71. [PubMed: 20383037]
59. Nakamura Y, Sanematsu K, Ohta R, Shirosaki S, Koyano K, Nonaka K, et al. Diurnal variation of human sweet taste recognition thresholds is correlated with plasma leptin levels. Diabetes. 2008; 57:2661–5. [PubMed: 18633111]
60. Shigemura N, Ohta R, Kusakabe Y, Miura H, Hino A, Koyano K, et al. Leptin modulates behavioral responses to sweet substances by influencing peripheral taste structures. Endocrinology. 2004; 145:839–47. [PubMed: 14592964]
61. Kawai K, Sugimoto K, Nakashima K, Miura H, Ninomiya YC. Leptin as a modulator of sweet taste sensitivities in mice. Proc Natl Acad Sci U S A. 2000; 97:11044–9. [PubMed: 10995460]
62. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007; 132:2131–57. [PubMed: 17498508]
63. Brubaker PL. The glucagon-like peptides: pleiotropic regulators of nutrient homeostasis. Ann N Y Acad Sci. 2006; 1070:10–26. [PubMed: 16888147]

64. Holst JJ, Orskov C, Nielsen OV, Schwartz TW. Truncated glucagon-like peptide I, an insulin-releasing hormone from the distal gut. FEBS Lett. 1987; 211:169–74. [PubMed: 3542566]

65. Maljaars PW, Peters HP, Mela DJ, Masclee AA. Ileal brake: a sensible food target for appetite control. A review. Physiol Behav. 2008; 95:271–81. [PubMed: 18692080]

66. Williams DL. Minireview: finding the sweet spot: peripheral versus central glucagon-like peptide 1 action in feeding and glucose homeostasis. Endocrinology. 2009; 150:2997–3001. [PubMed: 19389830]

67. Scrocchi LA, Brown TJ, MaClusky N, Brubaker PL, Auerbach AB, Joyner AL, et al. Glucose intolerance but normal satiety in mice with a null mutation in the glucagon-like peptide 1 receptor gene. Nat Med. 1996; 2:1254–8. [PubMed: 8898756]

68. Martin B, Dotson CD, Shin YK, Ji S, Drucker DJ, Maudsley S, et al. Modulation of taste sensitivity by GLP-1 signaling in taste buds. Ann N Y Acad Sci. 2009; 1170:98–101. [PubMed: 19686117]

69. Martin C, Passilly-Degrace P, Chevrot M, Ancel D, Sparks SM, Drucker DJ, et al. Lipid-mediated release of GLP-1 by mouse taste buds from circumvallate papillae: putative involvement of GPR120 and impact on taste sensitivity. J Lipid Res. 2012

70. Mathes CM, Bueter M, Smith KR, Lutz TA, le Roux CW, Spector AC. Roux-en-Y gastric bypass in rats increases sucrose taste-related motivated behavior independent of pharmacological GLP-1-receptor modulation. Am J Physiol Regul, Integr Comp Physiol. 2012; 302:R751–67. [PubMed: 22170618]

71. Unger RH, Cherrington AD. Glucagonocentric restructuring of diabetes: a pathophysiologic and therapeutic makeover. J Clin Invest. 2012; 122:4–12. [PubMed: 22214853]

72. Gelling RW, Vuguin PM, Du XQ, Cui L, Romer J, Pederson RA, et al. Pancreatic beta-cell overexpression of the glucagon receptor gene results in enhanced beta-cell function and mass. Am J Physiol Endocrinol Metab. 2009; 297:E695–707. [PubMed: 19602585]

73. Kieffer TJ, Heller RS, Unson CG, Weir GC, Habener JF. Distribution of glucagon receptors on hormone-specific endocrine cells of rat pancreatic islets. Endocrinology. 1996; 137:5119–25. [PubMed: 8895386]

74. Ma X, Zhang Y, Gromada J, Sewing S, Berggren PO, Buschard K, et al. Glucagon stimulates exocytosis in mouse and rat pancreatic alpha-cells by binding to glucagon receptors. Mol Endocrinol. 2005; 19:198–212. [PubMed: 15459251]

75. Brubaker PL, Drucker DJ. Structure-function of the glucagon receptor family of G protein-coupled receptors: the glucagon, GIP, GLP-1, and GLP-2 receptors. Receptors Channels. 2002; 8:179–88. [PubMed: 12529935]

76. Moran TH, Kinzig KP. Gastrointestinal satiety signals II. Cholecystokinin Am J Physiol Gastro Gastrointest Liver Physiol. 2004; 286:G183–8.

77. Staljanssens D, Azari EK, Christiaens O, Beaufays J, Lins L, Van Camp J, et al. The CCK(-like) receptor in the animal kingdom: functions, evolution and structures. Peptides. 2011; 32:607–19. [PubMed: 21167241]

78. Hajnal A, Covasa M, Bello NT. Altered taste sensitivity in obese, prediabetic OLETF rats lacking CCK-1 receptors. Am J Physiol Regul Integr Comp Physiol. 2005; 289:R1675–86. [PubMed: 16081877]

79. Said SI, Mutt V. Polypeptide with broad biological activity: isolation from small intestine. Science. 1970; 169:1217–8. [PubMed: 5450698]

80. Moody TW, Ito T, Osefo N, Jensen RT. VIP and PACAP: recent insights into their functions/roles in physiology and disease from molecular and genetic studies. Curr Opin in Endocrinol Diabetes Obes. 2011; 18:61–7. [PubMed: 21157320]

81. Fahrenkrug J. Transmitter role of vasoactive intestinal peptide. Pharmacol Toxicol. 1993; 72:354–63. [PubMed: 8103215]

82. Dickson L, Finlayson K. VPAC and PAC receptors: From ligands to function. Pharmacol Ther. 2009; 121:294–316. [PubMed: 19109992]

83. Kusakabe T, Matsuda H, Gono Y, Furukawa M, Hiruma H, Kawakami T, et al. Immunohistochemical localisation of regulatory neuropeptides in human circumvallate papillae. J Anat. 1998; 192 (Pt 4):557–64. [PubMed: 9723982]

84. Nguyen AD, Herzog H, Sainsbury A. Neuropeptide Y and peptide YY: important regulators of energy metabolism. Curr Opin Endocrinol Diabetes Obes. 2011; 18:56–60. [PubMed: 21157324]

85. Zhang L, Bijker MS, Herzog H. The neuropeptide Y system: pathophysiological and therapeutic implications in obesity and cancer. Pharmacol Ther. 2011; 131:91–113. [PubMed: 21439311]

86. Michel MC, Beck-Sickinger A, Cox H, Doods HN, Herzog H, Larhammar D, et al. XVI. International Union of Pharmacology recommendations for the nomenclature of neuropeptide Y, peptide YY, and pancreatic polypeptide receptors. Pharmacol Rev. 1998; 50:143–50. [PubMed: 9549761]

87. Tatemoto K, Carlquist M, Mutt V. Neuropeptide Y--a novel brain peptide with structural similarities to peptide YY and pancreatic polypeptide. Nature. 1982; 296:659–60. [PubMed: 6896083]

88. Chen CH, Stephens RL Jr, Rogers RC. PYY and NPY: control of gastric motility via action on Y1 and Y2 receptors in the DVC. Neurogastroenterol Motil. 1997; 9:109–16. [PubMed: 9198086]

89. Hastings JA, McClure-Sharp JM, Morris MJ. NPY Y1 receptors exert opposite effects on corticotropin releasing factor and noradrenaline overflow from the rat hypothalamus in vitro. Brain Res. 2001; 890:32–7. [PubMed: 11164766]

90. Leibowitz SF, Alexander JT. Analysis of neuropeptide Y-induced feeding: dissociation of Y1 and Y2 receptor effects on natural meal patterns. Peptides. 1991; 12:1251–60. [PubMed: 1667688]

91. Hurtado MD, Acosta A, Riveros PP, Baum BJ, Ukhanov K, Brown AR, et al. Distribution of y-receptors in murine lingual epithelia. PLoS One. 2012; 7:e46358. [PubMed: 23050020]

92. Hansel DE, Eipper BA, Ronnett GV. Neuropeptide Y functions as a neuroproliferative factor. Nature. 2001; 410:940–4. [PubMed: 11309620]

93. Michel MC, Fliers E, Van Noorden CJ. Dipeptidyl peptidase IV inhibitors in diabetes: more than inhibition of glucagon-like peptide-1 metabolism? Naunyn Schmiedebergs Arch Pharmacol. 2008; 377:205–7. [PubMed: 18398599]

94. Hartel S, Gossrau R, Hanski C, Reutter W. Dipeptidyl peptidase (DPP) IV in rat organs. Comparison of immunohistochemistry and activity histochemistry. Histochemistry. 1988; 89:151–61. [PubMed: 2456278]

95. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 1999; 402:656–60. [PubMed: 10604470]

96. Inui A, Asakawa A, Bowers CY, Mantovani G, Laviano A, Meguid MM, et al. Ghrelin, appetite, and gastric motility: the emerging role of the stomach as an endocrine organ. FASEB J. 2004; 18:439–56. [PubMed: 15003990]

97. Sato T, Nakamura Y, Shiimura Y, Ohgusu H, Kangawa K, Kojima M. Structure, regulation and function of ghrelin. J Biochem. 2012; 151:119–28. [PubMed: 22041973]

98. Tatemoto K, Rokaeus A, Jornvall H, McDonald TJ, Mutt V. Galanin - a novel biologically active peptide from porcine intestine. FEBS Lett. 1983; 164:124–8. [PubMed: 6197320]

99. Branchek TA, Smith KE, Gerald C, Walker MW. Galanin receptor subtypes. Trends Pharmacol Sci. 2000; 21:109–17. [PubMed: 10689365]

100. Waters SM, Krause JE. Distribution of galanin-1, -2 and -3 receptor messenger RNAs in central and peripheral rat tissues. Neuroscience. 2000; 95:265–71. [PubMed: 10619483]

101. Kaplan LM, Spindel ER, Isselbacher KJ, Chin WW. Tissue-specific expression of the rat galanin gene. Proc Natl Acad Sci U S A. 1988; 85:1065–9. [PubMed: 2448788]

102. Koegler FH, Ritter S. Galanin injection into the nucleus of the solitary tract stimulates feeding in rats with lesions of the paraventricular nucleus of the hypothalamus. Physiol Behav. 1998; 63:521–7. [PubMed: 9523894]

103. Wang S, Ghibaudi L, Hashemi T, He C, Strader C, Bayne M, et al. The GalR2 galanin receptor mediates galanin-induced jejunal contraction, but not feeding behavior, in the rat: differentiation of central and peripheral effects of receptor subtype activation. FEBS Lett. 1998; 434:277–82. [PubMed: 9742938]

104. Branchek T, Smith KE, Walker MW. Molecular biology and pharmacology of galanin receptors. Ann N Y Acad Sci. 1998; 863:94–107. [PubMed: 9928163]

105. Smith KE, Walker MW, Artymyshyn R, Bard J, Borowsky B, Tamm JA, et al. Cloned human and rat galanin GALR3 receptors. Pharmacology and activation of G-protein inwardly rectifying K+ channels. J Biol Chem. 1998; 273:23321–6. [PubMed: 9722565]

106. Mahoney SA, Hosking R, Farrant S, Holmes FE, Jacoby AS, Shine J, et al. The second galanin receptor GalR2 plays a key role in neurite outgrowth from adult sensory neurons. J Neurosci. 2003; 23:416–21. [PubMed: 12533601]

107. Bueter M, Miras AD, Chichger H, Fenske W, Ghatei MA, Bloom SR, et al. Alterations of sucrose preference after Roux-en-Y gastric bypass. Physiol Behav. 2011; 104:709–21. [PubMed: 21827777]

108. Miras AD, le Roux CW. Bariatric surgery and taste: novel mechanisms of weight loss. Curr Opin Gastroenterol. 2010; 26:140–5. [PubMed: 19901832]

109. Sinclair MS, Perea-Martinez I, Dvoryanchikov G, Yoshida M, Nishimori K, Roper SD, et al. Oxytocin signaling in mouse taste buds. PLoS One. 2010; 5:e11980. [PubMed: 20700536]

Highlights

- Taste cells express a number of bioactive peptides.
- These peptides are differentially distributed in the taste bud.
- Many have been implicated in the regulation of feeding or nutrient metabolism.
- Cognate receptors are also expressed in taste cells or on associated nerves.
- These peptides likely modulate taste function through local actions at the taste bud.

Table 1

Cellular localization of peptides in taste buds

Peptide	Taste Cell Type	Coexpressed Markers[a]	References
GLP-1	Type II	α-gustducin T1R3	40
	Type III	5-HT	
Glucagon	Type II	α-gustducin T1R3	40, 41
CCK	Type II	α-gustducin T1R2 VIP NPY	43, 44, 45
VIP	Type II	α-gustducin T1R2 CCK NPY	43, 45, 47, 83
NPY	Type II	CCK VIP	45
PYY	?	?	
Ghrelin	Type I	NTPDase	49
	Type II	PLCβ 2	
	Type III	α-gustducin NCAM	
	Type IV	PGP9.5 Shh[b]	
Galanin	Type II	PLCβ 2	50
	Type III	α-gustducin NCAM	

[a] all or a subset of peptide-expressing cells

[b] Shh, Sonic hedgehog

Table 2

Cellular localization of peptide receptors in taste buds

Peptide	Putative Receptor[a]	Receptor Location	Coexpressed Markers[b]	References
GLP-1	*Glp1r*	Intragemmal nerve fibers	PGP9.5	40
Glucagon	*Gcgr*	Type II cells	Glucagon 7B2 PLCβ 2 α-gustducin	41
CCK	*Cckar*	CCK+ taste cells	CCK	44
VIP	*Vpac1*	Type II cells	PLCβ 2	48
	Vpac2	Type II cells	PLCβ 2	
NPY	*Npy1r*	Type II cells		51, 91
	Npy2r	Taste cells		
	Ppyr1 (a.k.a. Npy4r)	Taste cells, nerve fibers	NCAM	
	Npy5r	Taste cells		
PYY	*Npy1r*	Taste cells		51, 91
	Npy2r	Taste cells		
	Ppyr1 (a.k.a. Npy4r)	Taste cells, nerve fibers	NCAM	
	Npy5r	Taste cells		
Ghrelin	*Ghsr*	Type I	NTPDase	49
		Type II	PLC β 2	
		Type III	α-gustducin NCAM	
		Type IV	PGP9.5 Shh[c]	
Galanin	*Galr2*	Taste buds		50

[a] gene nomenclature, *Mus musculus*

[b] all or a subset of receptor-expressing cells

[c] Shh, Sonic hedgehog

Table 3

Suggested functional roles of peptides produced in taste buds

Peptide	Signaling Mode[a]	Cellular Effects	Behavioral Effects[b]	References
GLP-1	paracrine	unknown	Maintain/enhance sweet responses; reduce umami responses	40, 68, 69
Glucagon	autocrine	unknown	Maintain/enhance sweet responses	41
CCK	autocrine	Decrease K^+ conductances; elevate $[Ca^{2+}]_i$	Decrease sweet, umami responses	44, 78
VIP	paracrine	unknown	Maintain/enhance sweet, sour responses Decrease bitter responses	48
NPY	paracrine	Enhance K^+ conductances	unknown	45
PYY	paracrine	unknown	unknown	46
Ghrelin	autocrine	unknown	Decrease salty, sour responses	49
Galanin	unknown	unknown	unknown	

[a] within taste buds; these receptors may also be targets of endocrine factors

[b] primarily inferred from genetic or pharmacological disruption of peptide production or receptor-dependent signaling