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Hormones in the naso-oropharynx: Endocrine modulation of taste and smell

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Abstract

Olfaction and gustation are important sensory modalities for locating food and for determining which foodstuffs to ingest. It is becoming apparent that there is a strong link between olfaction, gustation and metabolic control. Since endocrine signaling in the naso-oropharynx is likely to influence food intake, satiety and general metabolic control, it is potentially important to examine some of the major hormones that play an important role in energy homeostasis. Here, we provide an overview of the main endocrine factors that are known to be present in the naso-oropharynx and discuss their functional roles in maintaining metabolic function. Gaining a greater appreciation of how flavor perception is linked to peripheral metabolism could lead to novel therapeutic strategies for the treatment of obesity and life-style related diseases.

Introduction

The adequate ingestion of food and maintenance of energy homeostasis is crucial for an organism to survive, thrive and successfully reproduce. In mammals, there is a complex interplay between gustatory and olfactory sensory systems that each provides a gateway for monitoring and controlling food intake. The term 'taste' is used to refer to the mixture of sensations known as 'flavor perception' that include afferent information from the olfactory, gustatory and trigeminal nerves. Taste sensations arise from stimulation of the gustatory receptors located within the oropharyngeal mucosa. Transduction of olfactory information occurs when odorant molecules contact the dendrites of olfactory receptor neurons (ORN) residing in the olfactory epithelium, a specialized region of the dorsal nasal cavity. Olfaction and gustation are vital sensory modalities for locating food sources, determining which foodstuffs to ingest and for maintaining energy homeostasis. It is becoming apparent that there is a strong link between 'flavor perception' and metabolic control, and endocrine signaling within the taste buds of tongue and the olfactory bulb is likely to influence food intake, satiety and the general metabolic state. For example, several hormones crucial to the control of glucose/energy balance and appetite, *e.g.* the gut incretin, glucagon-like peptide-1, leptin, cholecystokinin and neuropeptide Y, are now thought to exert a strong local effect with respect to food perception and appreciation. This activity is mediated by their signaling roles in the

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gustatory and olfactory systems. The hormones and their cognate receptors that mediate this strong connection between somatic energy balance and food appreciation are listed in Table 1. In this review, we provide an overview of the main endocrine factors within the gustatory and olfactory systems and discuss some of the roles they play in maintaining energy balance. The peptide action in peripheral sensory structures (taste buds) will be compared to the action in central nervous system structures (olfaction).

The gustatory system: Basic taste modalities and signal transduction

Taste begins with molecular events at the surface membranes of modified epithelial cells that share many physical characteristics with neurons. Taste cells are organized into specialized structures known as taste buds within three types of papillae in the tongue (Figure 1). On the anterior two-thirds of the tongue, numerous fungiform papillae contain taste buds on their dorsal surface. In humans, each of these papillae contains about three to five taste buds, whereas in rodents there is typically a single taste bud on each fungiform papilla. On the posterior portion of the tongue, taste buds are contained in two types of papillae: the foliate papillae on the sides of the tongue and the circumvallate papillae along the posterior border, under the uvula. In humans, there are approximately 12 circumvallate papillae, whereas in rodents there is only one located on the midline, typically termed the vallate papilla. Taste cells are in a constant state of turnover, and new cells continuously arise from the division of basal cells within the taste bud and the adjacent epithelium. The average lifespan of a taste cell is approximately 9-10 days [1,2]. The exact mechanisms that regulate the continuous cell turnover are not clear, although it has been established that brain-derived neurotrophic factor (BDNF) is a crucial factor for initial development of taste papillae, taste buds, and their successful innervation by gustatory axons [3]. Mammalian taste cells are categorized into four cell types: type I, type II, type III, and basal or type IV cells [4]. The type I cells are thought to have secretory and supporting functions. Type II cells are thought to be the primary sensory receptor cells and typically express chemosensory signal transduction elements, such as gustducin and the T1R and T2R family of taste receptors [5,6,7]. The type III cells have afferent synaptic contact with nerve cells and are typically considered to be neuronal output cells. The type IV cells are rapidly dividing progenitor cells that differentiate into type I, type II or type III cells [4]. Immunocytochemical markers that distinguish among the different cell types are summarized in Table 2. The current consensus is that there are five basic tastes: sour, salty, sweet, umami, and bitter, where sour and salty tastants are modulated by ion channels and sweet, umami, and bitter tastants are transduced by G-protein coupled receptors.

Acidic and salt taste stimuli - Ion channels

Sour taste is elicited by acids (with citric acid being the prototype), and it is important for detecting unripened fruits and for maintaining an acid-base homeostasis within the body. The prototypical salty tastant is NaCl, and Na⁺ and Cl⁻ play important roles in maintaining blood volume and pressure. The taste apparatus for sour and salty taste are ion channels, which are present within the apical membrane of taste cells. The main group of ion channels that are involved in sour and salty taste transduction are members of the degenerin (DEG)/epithelial sodium channel (ENaC) superfamily. The Na⁺ ions diffuse through open ENaC channels and depolarize taste cells [8].

Sweet, umami and bitter taste stimuli - G protein-coupled receptors (GPCRs)

Many compounds elicit sweet taste, including sugars such as monosaccharides and disaccharides and sweeteners such as saccharin and sucralose [9]. Prototypic bitter tastants include amides such as denatonium benzoate and alkaloids such as caffeine and quinine. It is likely that bitter taste evolved to prevent ingestion of harmful foodstuffs. The prototypic compound that elicits the savory taste termed umami is monosodium glutamate (MSG). The

interaction between a taste stimulus and a taste receptor or apical channel produces depolarization of the taste receptor, resulting in activation of voltage-dependent ion channels within the cell and/or neurotransmitter release onto afferent gustatory nerve fibers. To date, three gene products have been shown to be responsible for the transduction of sweet and umami tastants. These genes, the TAS1Rs, encode functional GPCRs that have been demonstrated *in vitro* to bind sweet and umami stimuli [10,11,12,13,14]. The T1R receptors, of which there are three in mammals, are Class C GPCRs, which contain a large N-terminal domain that provides the binding site for many sweet ligands [15]. The T1R1 and T1R2 receptors are co-expressed with the T1R3 receptor (but not with each other), in different subsets of taste cells [14]. Additionally, the T1R1 and T1R3 together can form a functional receptor, which is responsive to umami stimuli but is not responsive to sweet stimuli. On the other hand, T1R2 and T1R3 form a heterodimer for sweet stimuli, including both nutritive and non-nutritive sweeteners [14,16,17]. Cells sensitive to bitter stimuli express small, overlapping subsets of different taste receptors, the T2Rs [5,18]. These are Class A GPCRs, of which there are at least 25 in mammals, that are characterized by a short N-terminal domain and individual taste cells tend to express multiple T2Rs [5]. Although many structures and receptors within the gustatory system have been thoroughly characterized, much less is known about the mechanistic transduction of taste stimuli, particularly regarding neuroendocrine control.

The olfactory system: System structure and organization

The olfactory system comprises one of the most complex and intricate signaling networks in mammals and it consists of several subsystems that are dedicated to distinct functional roles. The two major olfactory chemosensory subsystems are the vomeronasal organ (VNO) and the main olfactory epithelium (MOE). These two systems are localized in the nasal cavity but are functionally separate entities. The MOE is generally considered to be the primary organ responsible for sensing volatile odorants. These simplistic separations, however, may not fully describe the true complexity and interactivity of these systems or adequately describe their intricate substructures.

The mammalian MOE is comprised of several million olfactory sensory neurons (OSNs) and covers the turbinates in the posterior nasal cavity. The olfactory sensory neurons display a strong physical polarity in that they extend a single dendrite to the epithelial cell surface where each neuron presents many long cilia that are embedded in the nasal mucus. This wide array of cilia from the OSNs provides a vast surface for interaction with airborne odorant molecules. The ciliary plasma membrane of the OSNs possesses both the receptors and signal transduction machinery for the bulk of olfaction [19,20]. These odorant receptors (ORs) largely fall into the GPCR superfamily. Recent estimates place the total number of ORs at about 1000-1300 in rodents [21,22], while humans express around 300. Each OSN appears to possess just one OR, thus creating a vast, diverse array of sensory neurons in the turbinates [23,24]. Moreover, each OR seems capable of recognizing multiple odorant molecules, further increasing the signaling complexity in olfaction [25]. Separate OSNs that express the same OR project axons to common glomeruli in the main olfactory bulb (OB) (Figure 2). A population of OB interneurons that surround each olfactory glomerulus are called periglomerular (PG) cells. These cells integrate glomerular signaling, acting as regulators of the whole olfactory system via modulation of the first synaptic relay of the olfactory information from the olfactory nerve to the dendrites of the bulbar principal cells. These discrete and specific glomeruli are areas of intense synaptic connectivity and interaction between the axonal terminals of the OSNs and the dendritic trees of the olfactory bulb projection neurons. This convergence of OR-specific neuron populations with mutually exclusive glomeruli creates a 'chemospecific map' that engenders the ability to integrate combinatorial input from complex simultaneous odorant stimuli to identify and discriminate discrete odors [26].

Endocrine modulation of gustation and olfaction

A number of hormones are localized in subsets of taste cells and within structures of the olfactory system, and this list is rapidly expanding. We will provide an overview of the main hormones that are present within the gustatory and olfactory systems, with a special focus on hormonal modulation of gustatory information. Table 3 summarizes the hormones that will be discussed and their locations within the taste system, and Figures 1 and 2 show the locations of the hormones that we will discuss.

Glucagon-like peptide 1 (GLP-1) in taste

GLP-1 is synthesized in the enteroendocrine L cells of the gut and regulates numerous physiological processes, including insulin secretion and biosynthesis, gastric emptying, neuronal survival, and cardiac contractility [27,28]. GLP-1 is expressed in two distinct populations of taste cells: a subset of type II cells that co-express T1R3 and a subset of type III cells [29,30]. Mice lacking the GLP-1 receptor have significantly reduced taste sensitivity to both nutritive (sucrose) and nonnutritive sweeteners (sucralose). They also display a significant hypersensitivity to the umami tastant MSG [31] and a moderate increase in sensitivity to the sour tastant citric acid [29]. This indicates that GLP-1 produced in taste cells plays an important role in modulating taste sensitivity, namely the sweet and umami taste modalities. The presence of GLP-1 in taste cells highlights an interesting parallel between gustatory and intestinal epithelia. Other recent studies in rodents and humans have shown that many taste transduction molecules, including the T1R and T2R taste receptors, α -gustducin, phospholipase C- β 2 and the transient receptor potential M5 channel, are also expressed in subsets of cells in the stomach and intestine. Some of these cells have been identified as enteroendocrine L cells, which secrete GLP-1 in a T1R3- and α -gustducin-dependent manner in response to stimulation with sweet compounds [32].

GLP-1 in olfaction

Expression of mRNA for the GLP-1 precursor, pre-pro-glucagon (PPG), and the GLP-1 receptor has been demonstrated in the mammalian olfactory system [33]. PPG is localized to the glomerular layer of the olfactory bulb, while mRNA for the GLP-1 receptor has been found in the mitral cell layer of olfactory bulb. The presence of GLP-1R mRNA-containing cells in the mitral cell layer supports the notion that PPG mRNA-positive cells in the glomerular layer are interneurons and innervate mitral cells in the olfactory bulb. Via these interactions, GLP-1 may function as a neurotransmitter that directs information flow from the olfactory epithelium to the brain. It is interesting to note that recent advances in nasal peptide administration have demonstrated the ability of efficiently delivering GLP-1 and related peptides to the olfactory bulb [34], thus potentially facilitating the therapeutic modulation of olfactory processes with analogues of GLP-1. Such derivatives could be used for the treatment of disorders related to abnormal glucose control, such as type 2 diabetes.

Vasoactive Intestinal Peptide (VIP) in taste

Both GLP-1 and VIP belong to the PACAP/glucagon superfamily, have a similar expression pattern and bind to structurally similar receptors. VIP is widely present in the periphery as well as the central nervous system [35]. It is known to be a vasodilator, muscle relaxant, and stimulator of secretory activity [36]. More recently, the presence of VIP has been identified in taste cells in rat, hamster, carp, and human tongue [37,38,39]. However, a specific location and functional role of VIP in the taste buds remained unclear until a study by Shen and colleagues, who elucidated the expression pattern of VIP with the transduction markers α -gustducin, (which is involved in the modulation of both sweet and bitter tastants) and T1R2 (a transducer of sweet compounds). They reported that the majority of VIP-immunoreactive taste cells co-localized with α -gustducin, while a subset also expressed T1R2 [40]. Both α -gustducin

and T1R2 are markers for type II cells, implicating the presence of VIP in these taste cells of the tongue [41]. Based upon this expression pattern, it seems likely that VIP could be involved in the transduction of bitter and sweet stimuli [40].

VIP in olfaction

A subpopulation of short-axon cells located in the inframitral bulbar layers are generically named deep short-axon cells, which are opposed to those located in the layers above the mitral cells that are typically named superficial short-axon cells. Deep short-axon cells constitute a heterogeneous group of interneurons located in the internal plexiform layer (IPL), granule cell layer (GCL) and white matter (WM) [42]. Strong VIP immunoreactivity has been demonstrated in deep short-axon cells of the rat OB. It is assumed that deep short-axon cells innervate granule cells in the mammalian OB. VIP-containing deep short-axon cells are GABAergic interneurons, whose axons contact with the perisomatic region and the dendritic portions of subsets of deep short-axon cells that contain VIP, calbindin D-28k, and neuropeptide Y. These VIP-containing neurons form an interneuronal network that modulates the function of other interneurons different from granule cells. The modulation, therefore, of the OB by local circuits is more complex than the simple inhibition from PG cells and granule cells, reinforcing the importance of the contribution of other classes of GABAergic interneurons different from PG cells and granule cells to the bulbar circuitry [43]. Despite the clear and specific expression of VIP in the OB, the role of VIP in olfaction, however, remains unclear. Evidence from animals deficient in VIP has demonstrated alterations in their social interactivity, but these were not thought to be linked to specific olfactory discriminatory deficits [44].

Cholecystokinin (CCK) in taste

CCK is a multifunctional peptide which is expressed within the enteroendocrine cells of the small intestine, as well as in peripheral and central neurons, and plays a role in regulating gastric motility and pancreatic enzyme secretion. Expression of both CCK and VIP has been reported in taste cells of the rat, hamster, frog, and human [37,38,39,45]. CCK produces a number of subtle physiological actions on taste cells that are specifically mediated by CCKA receptors [45]. It is thought that CCK plays a role in modulating cell-to-cell communication within the taste bud. Shen and colleagues showed that CCK-expressing taste cells are present in the rat tongue and that CCK is co-expressed with specific taste signal transduction molecules [40]. They found that more than half (56%) of the CCK-expressing taste cells co-expressed α -gustducin mRNA, whereas far fewer (15%) co-expressed T1R2 mRNA. Interestingly, this study also showed that the majority of VIP-expressing taste cells co-expressed α -gustducin mRNA (60%), with only 19% of these cells co-expressing T1R2 mRNA [40]. Thus, CCK and VIP display very similar expression patterns with these signal transduction molecules, suggesting that they could both play a role in modulating taste perception.

CCK in olfaction

A role for CCK in olfaction was first proposed after CCK levels were shown to increase in the nucleus olfactorius anterior of rats that had been fed palatable food [46]. CCK interacts with two types of GPCRs: CCKA and CCKB [21,22]. Modulation of receptor activity strongly affects olfactory recognition of distinct odorants [47]. The functional relevance of CCK activity in olfaction seems tightly linked to social and reproductive behaviors [48]. Recent evidence identified the nature of CCK immunoreactive neuronal subsets in the olfactory system [49]. The olfactory glomeruli are arranged into a layer, the glomerular layer (GL), in the most superficial part of the OB (Figure 2). The specific activation of some olfactory receptors leads to a specific pattern of activation of different olfactory glomeruli with a topographically distinct locality in the GL, essentially constituting the 'chemosensory map' in the OB. Two types of PG cells are present in the rat, PG1 and PG2. The PG1 cells receive synaptic contacts from the

olfactory axons and are GABAergic while PG2 cells possess neither of these properties. CCK immunoreactivity is present exclusively in a selective subpopulation of PG cells that are GABA negative but do receive synaptic input from olfactory axons. It has been suggested that CCK released from these neurons may serve to control the activity and release of other neurotransmitters in the olfactory system such as dopamine [50] as there is close regulation of these two transmitters in other regions of the CNS. However, the functional role of CCK in olfaction has yet to be determined.

Neuropeptide Y (NPY) in taste

NPY is widely distributed throughout the mammalian brain and is one of the most potent orexigenic factors [51]. It is localized in type II cells and exerts inhibitory actions on single taste cells that are opposite in nature to those exerted by CCK [52]. NPY-expressing cells form a completely overlapping subset of CCK- and VIP-expressing taste cells, which suggests that these three factors could be playing important roles in information processing and autocrine/paracrine regulation of taste cells. The functional roles that these hormones play in gustatory function are presently unclear.

NPY in olfaction

In the nasal cavity, NPY was first identified in the olfactory bulb [53] and is now thought to be one of the most important modulators of the olfactory process. Studies on NPY function have concentrated on its connection to the unique regenerative capacity of the OB compared to other components of the central nervous system. NPY is thought to stimulate proliferation of olfactory precursor cells [54] and microvillar cells where it is proposed to have trophic influences in the regulation of olfactory receptor neuronal apoptosis and regeneration [55]. NPY is specifically expressed in the olfactory ensheathing cells of axon bundles, suggesting its involvement in the guidance and/or growth of ORN axons toward their target glomeruli in the olfactory bulb [56,57]. Specific genetic deletion of NPY in mice causes a dramatic reduction in the number of olfactory neuronal precursor cells, and null mice have considerably fewer olfactory receptor neurons than wild type mice [54,58]. The locus of NPY's action in the olfactory system has further been localized to activation of its cognate Y1 receptor subtype. NPY stimulation of the Y1 receptor on olfactory neurons or basal cells has been shown to activate mitogen-activated protein kinases during active neuroproliferation [54]. While there are strong links between the structure and maintenance of the olfactory system and NPY, a direct connection to specific odorant sensation modalities has yet to be fully established. Recent evidence has demonstrated that there are functional links between NPY expression and receptor activity in the olfactory epithelium of axolotl amphibian, related to their satiety status and behavior [59]. This suggests that NPY could play a role in modulating energy balance and requires further investigation.

Leptin in taste

Leptin, the product of the obese (ob) gene, is a hormone primarily produced in adipocytes. It plays a role in regulating food intake, energy expenditure, and body weight, mainly through its receptors in the hypothalamus but also to a lesser extent in some peripheral organs [60, 61]. The Ob receptor (Ob-R), especially the Ob-Rb, which is generally considered to be the signal-transducing receptor, is not only expressed in various regions within the CNS [62,63], but is also expressed in various peripheral cells, such as T cells [64] vascular endothelial cells, muscle cells [65], and pancreatic beta cells [66]. It has been demonstrated that a subset of taste cells express Ob-R, which indicates that taste cells are an additional peripheral site of leptin action [67]. Similar to pancreatic beta cells [68] and hypothalamic neurons [69], leptin has been shown to increase K⁺ conductance of taste cells, which results in hyperpolarization and reduction of cell excitability. It has been demonstrated by using lean and obese diabetic mice

that have a defect in their leptin receptor (db/db mice) that leptin plays a role in modulating sweet taste perception. The db/db mice display enhanced neural responses and elevated behavioral preferences to sweet stimuli [67]. Administration of leptin to lean mice suppressed the responses of the peripheral taste nerves to sweet substances, but had no effect on other taste modalities. This suppression of sweet taste perception by leptin could subsequently play a role in determining food/calorie intake.

Leptin in olfaction

The Ob-Rb leptin receptor is highly expressed in hypothalamic nuclei associated with the regulation of energy intake and expenditure, in central olfactory pathways including the nucleus of the lateral olfactory tract [70], and in central taste pathways such as the nucleus of the solitary tract in the brain stem [71]. Leptin and the leptin receptors have also been localized to the nasal mucosa. In the olfactory epithelium, immunoreactivity for the Ob-Rb is localized primarily in the supranuclear region of the sustentacular cells and/or duct cells of Bowman's glands at the surface of the epithelium [72]. The Ob-Rb has also been localized to the piriform cortex, an area involved in the relay of olfactory cues [73]. Interestingly, data has shown that serum levels of leptin are tightly connected to olfactory capacities in a gender-specific manner in humans. High odor discrimination capacities were associated with high serum leptin levels in men and low serum leptin levels in women [74]. This suggests that leptin may possess the ability to modulate olfactory-mediated pre-ingestive behavior.

Conclusions

It is clear that numerous common hormones are present within the gustatory and olfactory systems and that there is a highly complex and organized interplay between the different endocrine factors. The interplay between these systems modulates not only gustatory and olfactory function, but also whole-body physiological functions such as metabolic control and energy homeostasis. Many of the exact functional roles of these hormones remain to be established, as we have only reached the tip of the iceberg with regards to elucidating how these hormones modulate gustation and olfaction. From the functional roles that have been established so far, it is becoming apparent that hormones maintain similar functions at different target organs. The prime example so far is GLP-1, which modulates glycemic control in the periphery and modulates sweet taste perception in the tongue. Thus there seems to be a conservation of function through multiple layers of physiological systems, which from an evolutionary standpoint would create a more synergistic and efficient homeostatic and sensorial system. By gaining a better understanding about how these endocrine functions are conserved throughout different physiological modalities, we will obtain a better grasp of how complex higher order endocrine systems are organized, function, and how they could be pharmacologically manipulated to combat conditions such as obesity and type 2 diabetes. So far, research in this area is in its infancy and most likely the next few years will see a significant improvement in our knowledge of the function of hormones in the naso-oropharynx.

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Figure 1. Overview of the location of discussed hormones within the gustatory system

(a) The location of the various papillae of the tongue are shown. (b) The type of taste cell within the taste buds of the tongue and the corresponding hormones are shown. The arrows demarcate the location of each hormone within taste cell types I, II, III, and IV. Abbreviations: GLP-1, glucagon-like peptide 1; VIP, vasoactive intestinal peptide; CCK, cholecystokinin; NPY, neuropeptide Y; leptin-R, leptin receptor.

Figure 2. Overview of the location of discussed hormones within the olfactory system
 (a) The location of the olfactory bulb and various brain areas that are involved in olfaction are shown. (b) The hormones found in specific regions of the olfactory bulb are shown. The arrows demarcate the location of each hormone within this part of the olfactory system. Abbreviations: VIP, vasoactive intestinal peptide; GLP-1, glucagon-like peptide 1; GLP-1 R, glucagon-like peptide 1 receptor; NPY, neuropeptide Y.

Table 1
Ligands and their receptors: connecting food appreciation with energy metabolism

Ligands found in the gustatory and olfactory systems mediate important signaling mechanisms involved in both taste modulation and metabolic control, linking these processes in the body. Each ligand binds to its corresponding cognate receptor, initiating a primary signaling mechanism. Some ligands have overlapping receptor types and signaling mechanisms observed in both sensory modalities [75].

Ligand	Ligand type	Cognate receptor	Receptor type	Primary signaling mechanisms
Leptin	Polypeptide 167aa	LEPR/ Ob-R	Cytokine receptor	Jak-STAT activation
Glucagon-like peptide-1	Polypeptide 30aa	GLP-1-R	Class B 'secretin-like'	Gas AC activation
Vasoactive intestinal peptide	Polypeptide 28aa	VPAC1, VPAC2	Class B 'secretin-like'	VPAC1: Gas AC activation VPAC2: Gas AC activation + PLC/PLD
	Polypeptide 33aa	CCKA(1), CCKB(2)	Class A 'rhodopsin-like'	CCKA(0): Gαq PLC activation + Gas AC activation CCKB(2): Gαq PLC activation
Cholecystokinin				NPYIR: Gαi AC inhibition NPY2R: Gαq PLC activation NPY4R: Gαi AC inhibition + Gαq PLC activation NPY5R: Gαi AC inhibition
Neuropeptide Y	Polypeptide 36aa	NPY1, 2, 3, 4, 5-R	Class A 'rhodopsin-like'	
Sweet tastants	Sucrose/ sucralose	T1R2 + T1R3	Class C 'glutamate-like'	T1: gustducin, Gαi βγ mediated PLC activation
Umami tastants	Monosodium glutamate	T1R1 + T1R3	Class C 'glutamate-like'	T1: gustducin, Gαi βγ mediated PLC activation
Bitter tastants	Denatonium benzoate	T2R	Frizzled/TAS2R family	T2: gustducin, Gαi βγ mediated PLC activation

Table 2**Immunoreactive markers of the ultrastructural cell types found in taste receptor cells**

Type I cells primarily express neurotransmitter-related enzymes such as glutamate-aspartate transporter (GLAST) and nucleoside triphosphate diphosphohydrolase 2 (NTPDaseII). Type II cells express inositol triphosphate receptor 3 (IP₃R3), phospholipase C β 2 (PLC β 2), transient receptor potential channel M5 (TRPM5), and the G-protein subunit γ -13. A subset of type II cells (type II subset 1) expresses the G-protein subunit α -gustducin. Type III cells express aromatic L-amino acid decarboxylase (AADC), protein gene-related product 9.5 (PGP-9.5), brain-derived neurotrophic factor (BDNF), neural cell adhesion molecule (NCAM), synaptosome-associated protein 25 (SNAP-25), the putative sour receptor PKD2L1, and chromagranin A (CgA). There are two subsets of type III cells: one that shows immunoreactivity for γ -aminobutyric acid decarboxylase 67 (GAD67; also known as GAD1) (type III subset 1) and another for serotonin (5-HT) (type III subset 2). Type IV cells express sonic hedgehog (SHH) and prospero-related homeobox 1 (Prox1). For a comprehensive overview of the cell types and immunocytochemical markers see [76,77, 78,79].

Type I	Type II	Type III	Type IV
	T1R	AADC	
	T2R	PGP-9.5	
	IP ₃ R3	NCAM	
	PLC β 2	SNAP-25	
	TRPM5	PKD2L1	
	γ -13	CgA	
GLAST			SHH
NTPDase2	<u>Subset 1</u>	<u>Subset 1</u>	Prox1
	α -gustducin	GAD67	
		<u>Subset 2</u>	
		5-HT	

Table 3
Location of hormones/neuropeptides by cell type within taste buds
Vasoactive intestinal peptide (VIP), cholecystokinin (CCK), leptin receptor (leptin-R), and neuropeptide Y (NPY) are found within type II taste cells whereas glucagon-like peptide-1 (GLP) is found in both type II and III taste cells. Note that in the case of leptin, only the receptor, not the neuropeptide ligand, has been identified in the taste cells. The animal model in which the corresponding neuropeptide and type of cell(s) were discovered is also listed.

	Type I	Type II	Type III	Type IV	Reference
GLP-1		X (rat, mouse, monkey)	X (rat, mouse, monkey)		29
VIP		X (rat)			40
CCK		X (rat)			40
Leptin-R		X (mouse)			67
NPY		X (rat)			52