Review series

The cell biology of taste

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Taste buds are aggregates of 50–100 polarized neuroepithelial cells that detect nutrients and other compounds. Combined analyses of gene expression and cellular function reveal an elegant cellular organization within the taste bud. This review discusses the functional classes of taste cells, their cell biology, and current thinking on how taste information is transmitted to the brain.

Taste: our most intrepid sense

Sampling the environment through our sense of taste. Taste is the sensory modality that guides organisms to identify and consume nutrients while avoiding toxins and indigestible materials. For humans, this means recognizing and distinguishing sweet, umami, sour, salty, and bitter—the so-called "basic" tastes (Fig. 1). There are likely additional qualities such as fatty, metallic, and others that might also be considered basic tastes. Each of these is believed to represent different nutritional or physiological requirements or pose potential dietary hazards. Thus, sweet-tasting foods signal the presence of carbohydrates that serve as an energy source. Salty taste governs intake of Na^+ and other salts, essential for maintaining the body's water balance and blood circulation. We generally surmise that umami, the taste of L-glutamate and a few other L-amino acids, reflects a food's protein content. These stable amino acids and nucleotide monophosphates are naturally produced by hydrolysis during aging or curing. Bitter taste is innately aversive and is thought to guard against consuming poisons, many of which taste bitter to humans. Sour taste signals the presence of dietary acids. Because sour taste is generally aversive, we avoid ingesting excess acids and overloading the mechanisms that maintain acid–base balance for the body. Moreover, spoiled foods often are acidic and are thus avoided. Nonetheless, people learn to tolerate and even seek out certain bitter- and sour-tasting compounds such as caffeine and citric acid (e.g., in sweet-tart citrus fruits), overcoming innate taste responses. Variations of taste preference may arise from genetic differences in taste receptors and may have important consequences for food selection, nutrition, and health (Drayna, 2005; Kim and Drayna, 2005; Dotson et al., 2008; Shigemura et al., 2009).

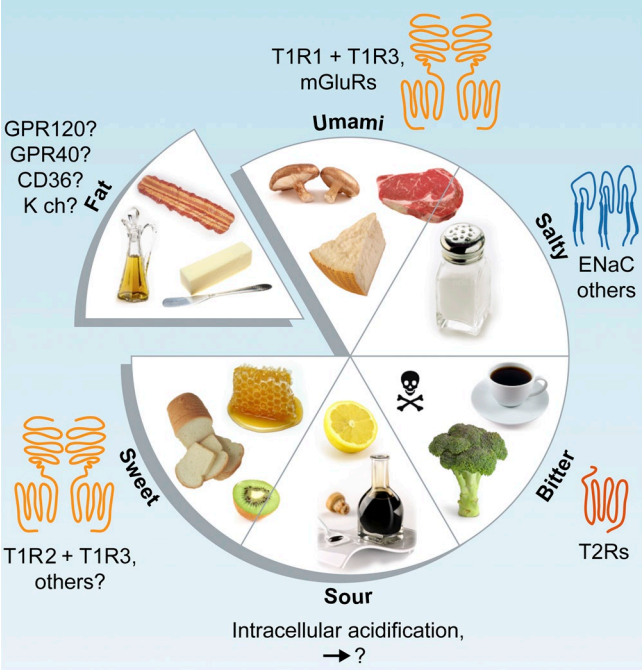

Figure 1. **Taste qualities, the taste receptors that detect them, and examples of natural stimuli.** Five recognized taste qualities—sweet, sour, bitter, salty, and umami—are detected by taste buds. Bitter taste is thought to protect against ingesting poisons, many of which taste bitter. Sweet taste signals sugars and carbohydrates. Umami taste is elicited by L-amino acids and nucleotides. Salty taste is generated mainly by Na^+ and sour taste potently by organic acids. Evidence is mounting that fat may also be detected by taste buds via dedicated receptors. The names of taste receptors and cartoons depicting their transmembrane topology are shown outside the perimeter. Bitter is transduced by G protein–coupled receptors similar to Class I GPCRs (with short extracellular N termini). In contrast, sweet and umami are detected by dimers of Class III GPCRs (with long N termini that form a globular extracellular ligand-binding domain). One of the receptors for Na^+ salts is a cation channel composed of three subunits, each with two transmembrane domains. Membrane receptors for sour and fat are as yet uncertain.

An important, if unrecognized aspect of taste is that it serves functions in addition to guiding dietary selection. Stimulating

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Glossary

Afferent	Neuron or nerve fiber that carries signals from peripheral sensory receptors to the central nervous system.
Autocrine	Referring to the action of a transmitter or hormone onto the same cell from which it was secreted.
Ecto-ATPase	An enzyme that degrades extracellular ATP; associated with the extracellular face of the plasma membrane of some taste bud cells.
GPCR	G protein–coupled receptor; integral plasma membrane proteins with 7 transmembrane domains; detect and signal neurotransmitters, hormones, sensory and other stimuli.
Gustation	The sense of taste; beginning with excitation of cells in taste buds and leading to perception of taste qualities (sweet, bitter, etc.).
Gustducin	Heterotrimeric G protein that includes a taste-selective Gα subunit, α-gustducin.
Pannexin	A family of ion channels (Panx1, 2, 3) related to the gap junction–forming connexin proteins; pannexins may only form hemichannels and transfer molecules from cytoplasm to extracellular space.
Paracrine	Referring to the action of a transmitter or hormone onto cells adjacent to or near the cell from which it was secreted.
Sensory code	The pattern of action potentials in sensory nerves that denotes the quality, intensity, duration, etc., of a sensory stimulus.
Somatosensory	The sense of pain, temperature, touch, pressure, texture (and other tactile stimuli).
T1Rs	A family of taste GPCRs (T1R1, R2, R3) that detect sweet or umami tastants; they function as heterodimers, e.g., T1R2 plus T1R3.
T2Rs	A family of taste GPCRs that detect bitter tastants; there are 20–40 members in different species.
Tastants	Compounds that elicit taste.
Taste GPCR	Families of GPCRs that are expressed in taste bud cells and bind sweet, bitter, or umami tastants.
Umami taste	A Japanese term ("good taste"), used for the taste of certain amino acids (especially glutamate), nucleotides (esp. IMP, GMP). Roughly translates as "savory".

taste buds initiates physiological reflexes that prepare the gut for absorption (releasing digestive enzymes, initiating peristalsis, increasing mesenteric flow) and other organs for metabolic adjustments (insulin release, sympathetic activation of brown adipose tissue, increased heart rate; Giduck et al., 1987; Mattes, 1997). Collectively, these reflexes that are triggered by the sensory (sight, smell, taste) recognition of food are termed cephalic phase responses.

Diverse sensory inputs tickle our taste buds. Taste is commonly confused with flavor, the combined sensory experience of olfaction and gustation. Gustatory signals originate in sensory end organs in the oral cavity—taste buds—and are triggered by water-soluble compounds that contact the apical tips of the epithelial cells of taste buds. In contrast, olfactory signals are generated by neurons in a specialized patch of nasal epithelium and are triggered by volatile compounds. Although the peripheral sensory organs for taste and smell are quite distinct, their signals are integrated in the orbitofrontal and other areas of the cerebral cortex to generate flavors and mediate food recognition (Rolls and Baylis, 1994; Small and Prescott, 2005).

Taste is also commonly confused with somatosensory sensations such as the cool of menthol or the heat of chili peppers. Strictly speaking, gustation is the sensory modality generated when chemicals activate oral taste buds and transmit signals to a specific region of the brainstem (the rostral solitary nucleus). Capsaicin (the active compound in chilies) and menthol principally stimulate ion channels in somatosensory nerve fibers (Caterina et al., 1997; McKemy et al., 2002). Capsaicin and related compounds may stimulate important interactions between somatosensory trigeminal (cranial nerve V) nerve fibers in the tongue and taste buds, and thus modulate taste (Wang et al., 1995; Whitehead et al., 1999). Additional somatosensory modalities such as texture and visual cues such as color also significantly influence the "taste" of foods (Small and Prescott, 2005).

Fatty taste lies at an intersection of somatosensory and gustatory perception. For many years, the recognition of dietary fat was considered primarily a function of its texture, and thus of somatosensory origin. Free fatty acids are potent gustatory stimuli (Gilbertson, 1998; Gilbertson et al., 2005; Laugerette et al., 2005). They are abundant in the human diet and, in some species, may be produced when salivary lipases rapidly hydrolyze ingested triglycerides in the oral cavity (Kawai and Fushiki, 2003). Specific membrane receptors essential for detecting fatty acids are present on taste bud cells (Laugerette et al., 2005; Sclafani et al., 2007; Wellendorph et al., 2009). Thus, fatty taste may also come to be recognized as another basic taste quality (Mattes, 2009).

In this review, we address only the molecular recognition and cellular processing that occurs in oral taste buds and that is conveyed in gustatory afferent nerves. Many of the proteins that underlie transduction for sweet, bitter, and umami tastes are also expressed in sensory cells lining the stomach and intestine. Chemosensory cells in the gut detect amino acids, peptides, sugars, and bitter compounds and respond by locally releasing peptides (e.g., GLP-1). These cells may also stimulate the vagus nerve that sends signals from the gut to the brain (Rozengurt and Sternini, 2007; Kokrashvili et al., 2009b). Yet, it is unlikely that this information contributes to the conscious perception or discrimination of sweet, sour, salty, etc., tastes. These "taste-like" chemosensory cells, although interesting and likely important, are not discussed further.

The structure of taste buds and other matters of taste

Taste buds are clusters of up to 100 polarized neuroepithelial cells that form compact, columnar pseudostratified "islands" embedded in the surrounding stratified epithelium of the oral

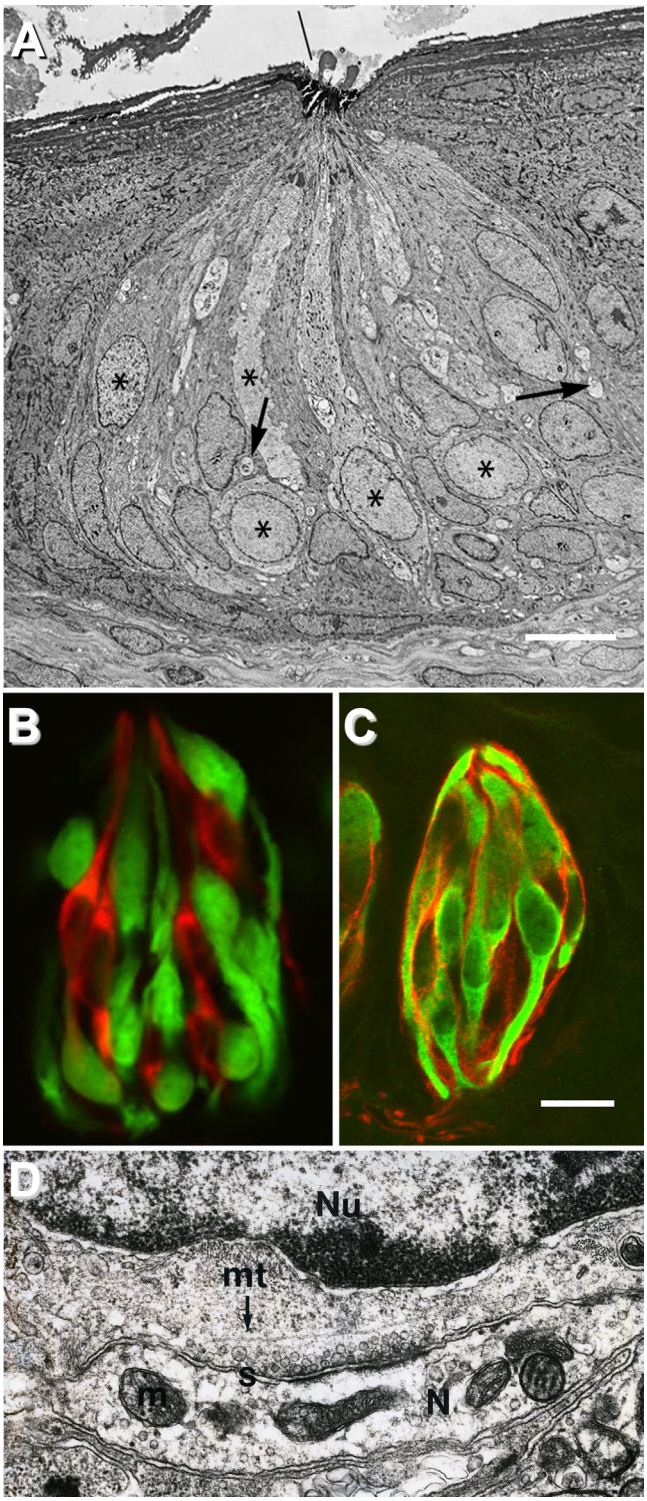


Figure 2. **Cell types and synapses in the taste bud.** (A) Electron micrograph of a rabbit taste bud showing cells with dark or light cytoplasm, and nerve profiles (arrows). Asterisks mark Type II (receptor) cells. Reprinted with permission from *J. Comp. Neurol.* (Royer and Kinnamon, 1991). (B) A taste bud from a transgenic mouse expressing GFP only in receptor (Type II) cells. Presynaptic cells are immunostained (red) for aromatic amino acid decarboxylase (a neurotransmitter-synthesizing enzyme that is a marker for these cells), and are distinct from receptor cells, identified by GFP (green). Reprinted with permission from *J. Neurosci.* (C) Taste buds immunostained for NTPDase2 (an ectonucleotidase associated with the plasma membrane of Type I cells) reveal the thin lamellae (red) of Type I cells. These cytoplasmic extensions wrap around other cells in the taste bud. GFP (green) indicates receptor cells as in B. Bar, 10 µm. Image courtesy of M.S. Sinclair and N. Chaudhari. (D) High magnification electron micrograph of a synapse between a presynaptic taste cell and a nerve terminal (N) in a hamster taste bud. The nucleus (Nu) of the presynaptic cell is at the top, and neurotransmitter vesicles cluster near the synapse(s). The nerve profile includes mitochondria (m) and electron-dense postsynaptic densities. mt, microtubule. Image courtesy of J.C. Kinnamon.

cavity (Fig. 2 A). In humans, there are ~5,000 taste buds in the oral cavity, situated on the superior surface of the tongue, on the palate, and on the epiglottis (Miller, 1995). Taste buds across the oral cavity serve similar functions. Although there are subtle regional differences in sensitivity to different compounds over the lingual surface, the oft-quoted concept of a "tongue map" defining distinct zones for sweet, bitter, salty, and sour has largely been discredited (Lindemann, 1999).

The elongate cells of taste buds are mature differentiated cells. Their apical tips directly contact the external environment in the oral cavity and thus experience wide fluctuations of tonicity and osmolarity, and the presence of potentially harmful compounds. Hence, taste bud cells, similar to olfactory neurons, comprise a continuously renewing population, quite unlike the sensory receptors for vision and hearing: photoreceptors and hair cells. It is now clear that adult taste buds are derived from local epithelium. At least some precursor cells are common between taste buds and the stratified nonsensory epithelium surrounding them (Stone et al., 1995; Okubo et al., 2009).

Tight junctions connecting the apical tips of cells were noted in electron micrographs of taste buds from several species (Murray, 1973, 1993). Typical tight junction components such as claudins and ZO-1 are detected at the apical junctions (Michlig et al., 2007). Taste buds, like most epithelia, impede the permeation of water and many solutes through their intercellular spaces. Nevertheless, paracellular pathways through taste buds have been demonstrated for certain ionic and nonpolar compounds (Ye et al., 1991). Indeed, permeation of Na^+ into the interstitial spaces within taste buds may contribute to the detection of salty taste (Simon, 1992; Rehnberg et al., 1993).

Considering the strongly polarized shapes of taste cells, relatively few proteins have been shown to be partitioned into the apical membrane. Examples include aquaporin-5 (Watson et al., 2007) and a K channel, ROMK (Dvoryanchikov et al., 2009).

Electron micrographs of taste buds reveal cells of varying electron densities that were interpreted as reflecting a continuum of stages of differentiation or maturation. However, precise morphometric analyses (i.e., electron density of cytoplasm, shape of nucleus, length and thickness of microvilli, and the presence of specialized chemical synapses) demonstrated that cells in taste buds were of discrete types (Murray, 1993; Pumplin et al., 1997; Yee et al., 2001). Ultrastructural features served as the basis for a reclassification of taste cells. Taste buds were described as containing cells imaginatively termed Types I, II, and III, and Basal, a nonpolarized, presumably undifferentiated cell, sometimes termed Type IV. What was missing was a convincing argument that these morphotypes represented distinct functional classes.

Subsequently, investigators have probed taste buds with antibodies at both light and electron microscopic levels, thus associating a few protein markers with the ultrastructurally defined cell types. These markers included α-gustducin (a taste-selective Gα subunit involved in taste transduction) in Type II cells and SNAP25 (a core component of SNARE complexes that regulate exocytosis of synaptic vesicles) in Type III cells (Yang et al., 2000; Yee et al., 2001; Clapp et al., 2004). Immunostaining in pairwise combinations then expanded the numbers of taste-specific proteins that could be assigned exclusively to cells of Type I, II, or III. Fig. 2 B demonstrates the clear distinction between cell Types II and III, with few if any cells exhibiting an intermediate pattern of gene expression. Similarly, cell Types I and II are separate populations (Fig. 2 C). Type III cells are the only cells that exhibit well-differentiated synapses (Fig. 2 D). An important advance has been with the generation of transgenic mice with GFP expressed from promoters selectively active in Type II or III cells. This has allowed a precise integration between functional properties, morphological features, and gene expression patterns of the cell types within taste buds. For instance, by combining patch-clamp and immunostaining on tissues from such mice, Medler et al. (2003) showed that voltage-gated Ca^{2+} currents, de rigeur components of synapses, are limited to the Type III cells. In contrast, Ca^{2+} imaging in combination with transgenic markers demonstrated that Type II cells respond to sweet, bitter, or umami taste stimuli while lacking voltage-gated Ca channels (Clapp et al., 2006; DeFazio et al., 2006).

Type I cells. Type I cells are the most abundant cells in taste buds, with extended cytoplasmic lamellae that engulf other cells (Fig. 2 C). Type I cells express GLAST, a transporter for glutamate, indicating that they may be involved in glutamate uptake (Lawton et al., 2000). Type I cells also express NTPDase2, a plasma membrane–bound nucleotidase that hydrolyzes extracellular ATP (Bartel et al., 2006). ATP serves as a neurotransmitter in taste buds (Finger et al., 2005) and glutamate also is a candidate neurotransmitter. Thus, Type I cells appear to be involved in terminating synaptic transmission and restricting the spread of transmitters, a role performed in the central nervous system by glial cells.

Type I cells also express ROMK, a K channel that may be involved in K^+ homeostasis within the taste bud (Dvoryanchikov et al., 2009). During prolonged trains of action potentials elicited by intense taste stimulation, Type I cells may serve to eliminate K^+ (see blue cell in Fig. 3) that would accumulate in the limited interstitial spaces of the taste bud and lead to diminished excitability of Type II and III cells. This is another stereotypic glial function. Patch-clamp studies have suggested that some taste cells, presumably Type I cells, possesses electrophysiological properties, such as inexcitability and high resting K^+ conductance, also characteristic of glia (Bigiani, 2001). Thus, Type I cells appear overall to function as glia in taste buds. A caveat is that not all Type I cells necessarily participate in each of the glial roles described above.

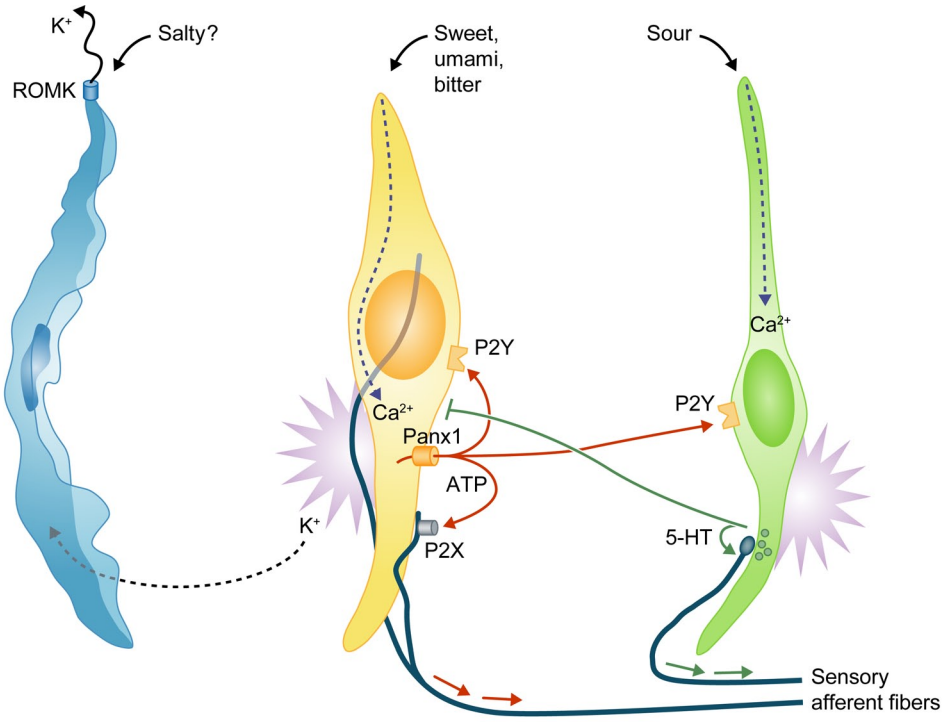
Lastly, Type I cells may exhibit ionic currents implicated in salt taste transduction (Vandenbeuch et al., 2008). Despite their being the most abundant cell type in taste buds, the least is known about Type I cells.

Type II (receptor) cells. There is little ambiguity in how Type II cells function within taste buds. Embedded in the plasma membrane of these cells are receptors that bind sweet, bitter, or umami compounds. These taste receptors are G protein–coupled receptors with seven transmembrane domains. Signaling events downstream of these receptors are well documented and are discussed under "Transduction" below (for review see Margolskee, 2002; Breslin and Huang, 2006; Simon et al., 2006). In addition, Type II cells express voltage-gated Na and K channels essential for producing action potentials, and hemichannel subunits, key players in taste-evoked secretion of ATP (yellow cell in Fig. 3). Any given Type II cell expresses taste GPCRs specific for only one taste quality, such as sweet or bitter, but not both (Nelson et al., 2001). Correspondingly, a given receptor cell responds only to stimulation with ligands that activate those receptors. In brief, Type II cells are "tuned" to sweet, bitter, or umami taste (Tomchik et al., 2007). In recognition of their role as the primary detectors of these classes of tastants, Type II cells were renamed "receptor" cells (DeFazio et al., 2006). Type II cells do not appear to be directly stimulated by sour or salty stimuli.

Curiously, receptor cells do not form ultrastructurally identifiable synapses. Instead, nerve fibers, presumably gustatory afferents, are closely apposed to these cells (Murray, 1973, 1993; Yang et al., 2000; Yee et al., 2001; Clapp et al., 2004). Signals transmitted from receptor cells to sensory afferents or other cells within the taste bud must do so by unconventional mechanisms, i.e., without the involvement of synaptic vesicles, as will be described below.

Type III (presynaptic) cells. The consensus is that Type III cells (green cell in Fig. 3) express proteins associated with synapses and that they form synaptic junctions with nerve terminals (Murray et al., 1969; Murray, 1973, 1993; Yang et al., 2000; Yee et al., 2001). These cells express a number of neuronal-like genes including NCAM, a cell surface adhesion molecule, enzymes for the synthesis of at least two neurotransmitters, and voltage-gated Ca channels typically associated with neurotransmitter release (DeFazio et al., 2006; Dvoryanchikov et al., 2007). Type III cells, expressing synaptic proteins and showing depolarization-dependent Ca^{2+} transients typical of synapses, have been labeled "presynaptic" cells (DeFazio et al., 2006). Like receptor cells, presynaptic cells also are excitable and express a complement of voltage-gated Na and K channels to support action potentials (Medler et al., 2003; Gao et al., 2009; Vandenbeuch and Kinnamon, 2009a,b). The origin of nerve fibers that synapse with Type III cells, and whether they represent taste afferents, is not known. In addition to these neuronal properties, presynaptic cells also respond directly to sour taste stimuli and carbonated solutions and are presumably the cells responsible for signaling these sensations (Huang et al., 2006; Tomchik et al., 2007; Huang et al., 2008b; Chandrashekar et al., 2009).

A key feature of presynaptic cells is that they receive input from and integrate signals generated by receptor cells (see below). Hence, in the intact taste bud, unlike receptor cells, presynaptic cells are not tuned to specific taste qualities but instead respond broadly to sweet, salty, sour, bitter, and umami compounds (Tomchik et al., 2007). Although presynaptic cells share many



Type I glial-like cell	
Neurotransmitter clearance	
GLAST	Glutamate reuptake
NTPDase2	Ecto-ATPase
NET	Norepinephrine uptake
Ion redistribution and transport	
ROMK	K^+ homeostasis
Other	
OXTR	Oxytocin signaling?

Type II receptor cell	
Taste transduction	
T1Rs, T2Rs	Taste GPCRs
mGluRs	Taste GPCRs
Gα-gus, Gγ13	G protein subunits
PLCβ2	Synthesis of IP3
TRPM5	Depolarizing cation current
Excitation and transmitter release	
$Na_v1.7$, $Na_v1.3$	Action potential generation
Panx1	ATP release channel

Type III presynaptic cell	
Surface glycoproteins, ion channels	
NCAM	Neuronal adhesion
PKD channels	Sour taste?
Neurotransmitter synthesis	
AADC	Biogenic amine synthesis
GAD67	GABA synthesis
5-HT	Neurotransmitter
Chromogranin	Vesicle packaging
Excitation, transmitter release	
$Na_v1.2$	Action potential generation
$Ca_v2.1$, $Ca_v1.2$	Voltage-gated Ca^{2+} current
SNAP25	SNARE protein, exocytosis

Figure 3. **The three major classes of taste cells.** This classification incorporates ultrastructural features, patterns of gene expression, and the functions of each of Types I, II (receptor), and III (presynaptic) taste cells. Type I cells (blue) degrade or absorb neurotransmitters. They also may clear extracellular K^+ that accumulates after action potentials (shown as bursts) in receptor (yellow) and presynaptic (green) cells. K^+ may be extruded through an apical K channel such as ROMK. Salty taste may be transduced by some Type I cells, but this remains uncertain. Sweet, bitter, and umami taste compounds activate receptor cells, inducing them to release ATP through pannexin1 (Panx1) hemichannels. The extracellular ATP excites ATP receptors (P2X, P2Y) on sensory nerve fibers and on taste cells. Presynaptic cells, in turn, release serotonin (5-HT), which inhibits receptor cells. Sour stimuli (and carbonation, not depicted) directly activate presynaptic cells. Only presynaptic cells form ultrastructurally identifiable synapses with nerves. Tables below the cells list some of the proteins that are expressed in a cell type–selective manner.

neuron-like properties, it is clear that they are not a homogeneous population (Tomchik et al., 2007; Roberts et al., 2009).

Basal cells. This category describes spherical or ovoid cells that do not extend processes into the taste pore and are likely to be undifferentiated or immature taste cells (Farbman, 1965). It is not clear whether all basal cells within taste buds represent a common undifferentiated class of cells. Unambiguous markers for these cells have not been identified, and the exact significance of basal cells as a cell population remains to be elucidated.

Nerve fibers. Taste buds are innervated by sensory neurons whose cell bodies are located in clusters nestled against the brain (the geniculate, petrosal, and nodose cranial ganglia). In the adult, each taste bud is innervated by 3–14 sensory ganglion neurons, depending on the species (mouse, rat, hamster) and oral region (tongue, palate; Krimm and Hill, 1998; Whitehead et al., 1999). Gustatory nerve fibers comingle with a rich plexus of other nerve fibers under the taste epithelium. In the absence of clear markers to distinguish them, one cannot discern which of these fibers carry taste information as opposed to pain,

tactile, or thermal signals. Taste axons branch and penetrate the basal lamina to enter taste buds. Although some fibers terminate in synaptic structures on Type III cells, others course intimately among taste cells without forming specialized synapses (Farbman, 1965; Murray et al., 1969; Murray, 1973).

As will be explained next, the concerted action of Type I, Type II (receptor), and Type III (presynaptic) cells underlies taste reception. There are synaptic interactions, both feed-forward and feedback, between these cells when taste stimuli activate the taste bud.

Beyond the tasty morsel: the underlying molecular mechanisms for nutrient detection

Transduction of gustatory stimuli in receptor (Type II) cells. As stated above, sweet, umami, and bitter compounds each activate different taste GPCRs that are expressed in discrete sets of receptor cells. For instance, receptor cells that express members of the T2R family of GPCRs sense bitter compounds (Chandrashekar et al., 2000). In different mammals, 20–35 separate genes encode members of the T2R family. These taste receptors exhibit heterogeneous molecular receptive ranges: some are narrowly tuned to 2–4 bitter-tasting compounds, whereas others are promiscuously activated by numerous ligands (Meyerhof et al., 2010). On the basis of in situ hybridizations with mixed probes on rodent taste buds, the T2Rs were reported either to be expressed as overlapping subsets of mRNAs (Matsunami et al., 2000) or coexpressed in a single population of taste cells (Adler et al., 2000). More recently, detailed analyses on human taste buds confirm that different bitter-responsive taste cells express subsets of 4–11 of the T2Rs in partially overlapping fashion (Behrens et al., 2007). This observation is important insofar as it provides a molecular basis for discriminating between different bitter compounds. Bitter-sensing taste cells are known to functionally discriminate among bitter compounds (Caicedo and Roper, 2001). This pattern of T2R expression, along with polymorphisms across the gene family, is thought to allow humans and animals to detect the enormous range of potentially toxic bitter compounds found in nature (Drayna, 2005).

Receptor cells expressing the heterodimer T1R2+T1R3 respond to sugars, synthetic sweeteners, and sweet-tasting proteins such as monellin and brazzein (Nelson et al., 2001; Jiang et al., 2004; Xu et al., 2004). Although the persistence of sensitivity to some sugars in mice lacking T1R3 suggests that additional receptors for sweet may exist (Damak et al., 2003), candidate receptors have yet to be identified.

A third class of receptor cells expresses the heterodimeric GPCR, T1R1+T1R3, which responds to umami stimuli, particularly the combination of L-glutamate and GMP/IMP, compounds that accumulate in many foods after hydrolysis of proteins and NTPs (Li et al., 2002; Nelson et al., 2002). Nevertheless, robust physiological responses and behavioral preference for umami tastants persist in mice in which T1R3 is knocked out, suggesting that additional taste receptors may contribute to umami detection (Damak et al., 2003; Maruyama et al., 2006; Yasumatsu et al., 2009). Functional responses to various umami tastants occur in distinct subsets of cells within taste buds (Maruyama et al., 2006) and neural responses show similarly heterogeneous patterns (Yoshida et al., 2009b), observations that further suggest that umami taste is complex, and likely mediated through multiple types of taste receptors. In summary, although the T1R1+T1R3 dimer clearly acts as an umami receptor, additional GPCRs may play complementary roles. Candidates for additional umami receptors include a taste-specific variant or other isoforms of G protein–coupled glutamate receptors expressed in taste buds (Chaudhari et al., 2000; Li et al., 2002; Nelson et al., 2002; San Gabriel et al., 2009).

The T1Rs are dimeric Class III GPCRs, with large N-terminal extracellular domains (Max et al., 2001). This domain forms a Venus Flytrap structure as in other family members. T1Rs also possess a multitude of additional ligand-binding sites on the exterior faces of the flytrap, in the linker, and perhaps even in the plane of the membrane (Cui et al., 2006; Temussi, 2009). In contrast, T2Rs resemble Class I GPCRs with binding sites in the transmembrane helices, in keeping with the nonpolar nature of many bitter ligands (Floriano et al., 2006).

When they bind taste molecules, taste GPCRs activate heterotrimeric GTP-binding proteins (Fig. 4 A). For example, the bitter receptors (T2Rs) are coexpressed with and activate the taste-selective Gα subunit, α-gustducin, and the closely related α-transducin (Ruiz-Avila et al., 1995). Taste receptors that include T1R3 may couple to Gα14 and other Gα subunits (Tizzano et al., 2008). Despite this apparent selectivity of taste GPCRs for Gα subunits, the principal pathway for taste transduction appears to be via Gβγ, including Gγ13 and Gβ1 or Gβ3 (Huang et al., 1999). Upon ligand binding, the Gβγ subunits are freed from the taste GPCR and interact functionally with a phospholipase, PLCβ2, an unusual isoform that is activated by Gβγ rather than the more common Gαq family subunits (Rössler et al., 1998). Knocking out PLCβ2 severely diminishes, but does not eliminate taste sensitivity (Zhang et al., 2003; Dotson et al., 2005). PLCβ2 stimulates the synthesis of IP_3, which opens IP_3R3 ion channels on the endoplasmic reticulum, releasing Ca^{2+} into the cytosol of receptor cells (Simon et al., 2006; Roper, 2007). The elevated intracellular Ca^{2+} appears to have two targets in the plasma membrane: a taste-selective cation channel, TRPM5, and a gap junction hemichannel, both found in receptor cells (Pérez et al., 2002; Huang et al., 2007). The Ca^{2+}-dependent opening of TRPM5 produces a depolarizing generator potential in receptor cells (Liu and Liman, 2003). If sufficiently large, generator potentials evoke action potentials in receptor cells. The two signals elicited by tastants: strong depolarization and increased cytoplasmic Ca^{2+}, are integrated by gap junction hemichannels. The outcome of this convergence is that the taste bud transmitter, ATP, and possibly other molecules, are secreted through the hemichannel pores into the extracellular space surrounding the activated receptor cell (Fig. 3, yellow cell; and Fig. 4 A; Huang et al., 2007; Romanov et al., 2007; Huang and Roper, 2010).

Although most researchers agree that ATP release occurs through a plasma membrane hemichannel, whether these channels are formed of pannexin (Panx) or connexin (Cx) subunits is not fully resolved. Panx1 is robustly expressed in receptor cells,

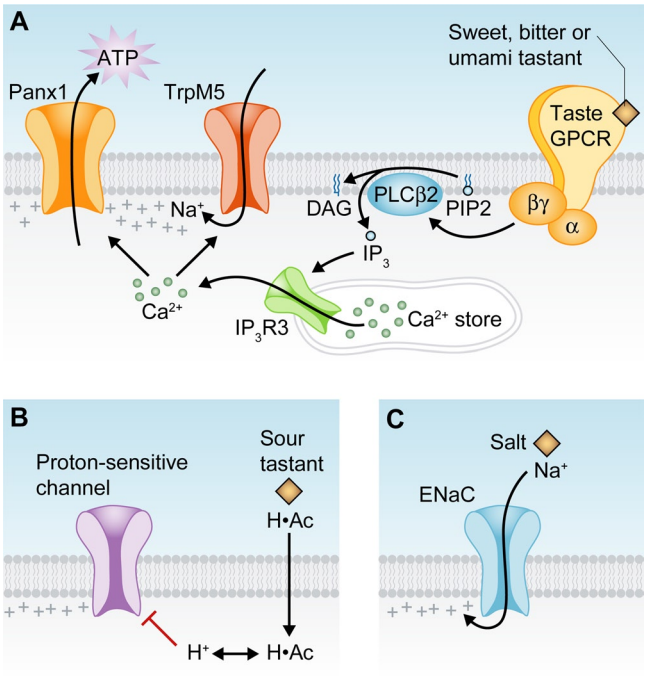


Figure 4. **Mechanisms by which five taste qualities are transduced in taste cells.** (A) In receptor (Type II) cells, sweet, bitter, and umami ligands bind taste GPCRs, and activate a phosphoinositide pathway that elevates cytoplasmic Ca^{2+} and depolarizes the membrane via a cation channel, TrpM5. The combined action of elevated Ca^{2+} and membrane depolarization opens the large pores of gap junction hemichannels, likely composed of Panx1, resulting in ATP release. Shown here is a dimer of T1R taste GPCRs (sweet, umami). T2R taste GPCRs (bitter) do not have extensive extracellular domains and it is not known whether T2Rs form multimers. (B) In presynaptic (Type III) cells, organic acids (HAc) permeate through the plasma membrane and acidify the cytoplasm where they dissociate to acidify the cytosol. Intracellular H^+ is believed to block a proton-sensitive K channel (as yet unidentified) and depolarize the membrane. Voltage-gated Ca channels would then elevate cytoplasmic Ca^{2+} to trigger exocytosis of synaptic vesicles (not depicted). (C) The salty taste of Na^+ is detected by direct permeation of Na^+ ions through membrane ion channels, including ENaC, to depolarize the membrane. The cell type underlying salty taste has not been definitively identified.

whereas several Cx subunits are expressed at more modest levels (Huang et al., 2007; Romanov et al., 2007). Although there may be gap junctions presumably formed of connexins between cells in mammalian taste buds (Yoshii, 2005), such junctions would not be expected to secrete ATP into extracellular spaces. A principal argument for Cx hemichannels in taste cells was based on the blocking action of certain isoform-selective mimetic peptides. However, the specificity of such peptides has recently been called into question (Wang et al., 2007). Finally, Panx1 hemichannels are gated open by elevated cytoplasmic Ca^{2+} and/or membrane depolarization (Locovei et al., 2006). ATP release from taste cells similarly is mediated by both Ca^{2+} and voltage (Huang and Roper, 2010). In contrast, Cx hemichannels usually open only in the absence of extracellular Ca^{2+} and typically are blocked by elevated cytoplasmic Ca^{2+}. Further, Panx1-selective antagonists block taste-evoked ATP secretion (Huang et al., 2007; Dando and Roper, 2009). Thus, the weight of the evidence strongly favors ATP release through Panx1 hemichannels in receptor cells. Nevertheless, the ideal test to resolve this question, namely testing ATP release from taste cells from Panx1 or Cx knockout mice, has yet to be reported.

Presynaptic (Type III) cells also detect some taste stimuli. Presynaptic cells exhibit very different taste sensitivity and transduction mechanisms when compared with receptor cells. Sour taste stimuli (acids) excite presynaptic cells (Tomchik et al., 2007). The membrane receptor or ion channel that transduces acid stimuli remains as yet unidentified. Nonselective cation channels formed by PKD2L1 and PKD1L3 were proposed as candidate sour taste receptors (Huang et al., 2006; Ishimaru et al., 2006; LopezJimenez et al., 2006). Yet, this channel is sensitive to extracellular pH rather than a drop in cytoplasmic pH, which is known to be the proximate stimulus for sour taste (Fig. 4 B; Lyall et al., 2001; Huang et al., 2008b). Further, mice lacking PKD1L3 remain capable of detecting acid taste stimuli (Nelson et al., 2010). More likely candidate acid receptors in Type III cells are plasma membrane channels that are modulated by cytoplasmic acidification, such as certain K channels (Lin et al., 2004; Richter et al., 2004). Presynaptic cells also detect carbonation, partly through the action of carbonic anhydrase that produces protons and thus acidifies the environment (Graber and Kelleher, 1988; Simons et al., 1999; Chandrashekar et al., 2009). The complete transduction pathways for carbonation and sour taste have not been completely described.

Salt detection and transduction. Taste buds detect Na salts by directly permeating Na^+ through apical ion channels and depolarizing taste cells. An ion channel that has long been thought to mediate this action is the amiloride-sensitive epithelial Na channel, ENaC (Fig. 4 C; Heck et al., 1984; Lin et al., 1999; Lindemann, 2001). This notion was recently confirmed by knocking out a critical ENaC subunit in taste buds, which impaired salt taste detection (Chandrashekar et al., 2010). This study did not assign salt sensitivity to any of the established taste cell types, but patch-clamp studies suggested that Na^+-detecting cells are Type I cells (Vandenbeuch et al., 2008). Pharmacological and other evidence suggests that salt transduction in human and animal models also occurs via additional membrane receptors or ion channels. Although a modified TrpV1 channel has been proposed as a candidate Na^+ taste transducer, knockout mice show a minimal phenotype with respect to salt detection (Ruiz et al., 2006; Treesukosol et al., 2007).

Information processing and cell-to-cell signaling in taste buds: teasing apart our taste response

Transmitters and information flow. Receptor and presynaptic cells each release different neurotransmitters (Huang et al., 2007). To date, receptor cells are known to release only ATP, via pannexin channels as described above. Presynaptic cells on the other hand, secrete serotonin (5-HT) and norepinephrine (NE). In some instances presynaptic cells co-release both these amines (Dvoryanchikov et al., 2007; Huang et al., 2008a). Secretion of these biogenic amines appears to be via conventional Ca^{2+}-dependent exocytosis. Clusters of monoaminergic vesicles are present at synapses in electron micrographs of mouse presynaptic cells (Takeda and Kitao, 1980).

Gustatory stimuli initiate a sequence of chemical signals that are passed between cells in the taste bud. When sweet, bitter, or umami tastants excite taste buds, ATP secreted from receptor cells stimulates gustatory afferent nerve fibers. At the same time, ATP also excites adjacent presynaptic cells and stimulates them to release 5-HT and/or NE. ATP secreted during taste stimulation has a third target, namely the receptor cells, themselves. ATP, acting as an autocrine transmitter, exerts positive feedback onto receptor cells, increasing its own secretion and presumably counteracting its degradation by ecto-ATPase (Huang et al., 2009; Fig. 3).

The 5-HT released by presynaptic cells also may have multiple targets. One effect of 5-HT is to inhibit receptor cells. That is, 5-HT exerts a negative feedback onto receptor cells. The opposing effects of positive (purinergic autocrine) and negative (serotonergic paracrine) feedback in the taste bud during gustatory activation combine to shape the signals transmitted from taste buds to the hindbrain. However, details of how these feedback pathways are balanced to shape the eventual sensory output awaits experimentation and many questions remain. One might speculate that 5-HT mediates "lateral inhibition," suppressing the output of adjacent receptor (e.g., bitter) cells when a particular (e.g., sweet) receptor cell is stimulated. Alternatively, the negative feedback loop may participate in sensory adaptation by decreasing the afferent signal over time.

Other sites of action for 5-HT (and NE) possibly include the nerve fibers that form synapses with presynaptic taste cells. Quite possibly, there are parallel purinergic and serotonergic outputs from taste buds and parallel information pathways leading into the hindbrain. At present, this is only a speculation (Roper, 2009).

In summary (see Fig. 3), receptor cells detect and discriminate sweet, bitter, or umami tastants, generate Ca^{2+} signals, and release ATP transmitter onto afferent nerves. The ATP from different receptor cells converges onto and produces secondary excitation of presynaptic cells, thereby integrating signals representing all three taste qualities (Tomchik et al., 2007). It is not clear that the secondary responses of presynaptic cells to sweet, bitter, and umami stimuli are necessary for identifying or discriminating these taste qualities. Primary signals in presynaptic cells are only generated by sour tastants, and this is the only quality that is lost when presynaptic cells are ablated (Huang et al., 2006).

Cracking the taste code. Taste afferent nerve fibers transmit information from taste buds to the brain. How the activation of receptor and presynaptic cells during gustatory stimulation translates into a neural code that specifies different taste qualities (sweet, bitter, etc.) remains unclear. Two opposing solutions to this logic problem are much discussed. On the one hand, dedicated nerve fibers ("labeled lines") could transmit each quality, e.g., "bitter" cells, "bitter" fibers, and "bitter" neurons at each successive relay in the brain. On the other hand, a combinatorial system would have qualities encoded by patterns of activity across several fibers. In the latter case, any given fiber could transmit information for more than a single quality. A third, less-discussed option is a temporal code in which quality would be denoted by a timing pattern of action potentials such as occurs in auditory fibers.

The question of coding has been addressed through genetic manipulations and physiological and behavioral assays. Electrophysiological recordings from single afferent fibers or their parent sensory ganglion cells indicated that some neurons respond strongly to a single taste quality (usually sweet), but also have weak responses to other tastes. In contrast, other afferent neurons are excited by multiple tastes, i.e., are broadly responsive (Hellekant et al., 1997; Frank et al., 2008; Breza et al., 2010). Thus, afferent taste neurons show response profiles similar to both narrowly tuned taste bud receptor cells and to broadly tuned presynaptic cells. The pattern of afferent neuron activity mirrors the heterogeneity of taste bud cellular responses (Gilbertson et al., 2001; Caicedo et al., 2002; Tomchik et al., 2007; Yoshida et al., 2009a; Breza et al., 2010) and suggests that neural activity encoding taste does not follow a simple dedicated labeled-line logic. That is, "bitter-specific," "sour-specific," etc., afferent sensory fibers and subsequent neurons in the network—obligatory components of labeled-line coding—have never been reported.

An argument for labeled-line coding has been made based on the results of replacing a modified opioid receptor for the bitter or sweet receptors in taste cells (Zhao et al., 2003; Mueller et al., 2005). Mice engineered with this foreign receptor in "sweet" receptor cells strongly preferred and copiously drank solutions of a synthetic ligand for the modified receptor, as if the compound tasted sweet. For normal mice, the ligand was tasteless. Conversely, when the opioid receptor was targeted to "bitter" receptor cells, the same ligand was strongly aversive. Although this was presented as firm proof of labeled-line coding, the logic bears reexamining. Take for example a computer keyboard. Striking the "A" key activates a combination of electronic signals that results in the illumination of a combination of pixels to produce the first letter of the alphabet on screen. If the plastic key (the "receptor") on the keyboard were changed, striking the replacement key would still produce the letter "A" on screen. The experiment does not inform one about the electronic coding that is out of sight between the two visible events, and does not imply that labeled wires link the base of the key to particular pixels. Chemosensory researchers agree that labeled taste cells exist. Labeled lines remain controversial.

In summary, sweet, bitter, and umami cells all secrete the same neurotransmitter, ATP, onto afferent fibers. Discrete synapses are lacking that might couple receptor cells with sensory afferent fibers to transmit single taste qualities. Although some taste cells and sensory afferent neurons are tightly tuned, others are responsive to multiple taste qualities. Thus, it remains an open question exactly how information gathered by well-differentiated receptor cells in taste buds is "coded" for the eventual perception of distinct taste qualities.

Future directions in taste research

Taste research, although making tremendous strides in recent years, has exposed major gaps in our understanding. Among the open questions is the molecular identification of additional taste receptors. Known taste receptors do not account for all ligands and sensory characteristics for sweet and umami tastes. It is likely that there are additional, undiscovered sweet and umami

receptors (Chaudhari et al., 2009). There is also the question of transduction mechanisms for some of the less-studied qualities such as sour, fatty, metallic, and astringent. Solving these may require combining molecular and population genetic analyses on human or mouse populations along with more conventional expression studies.

Another area of intense investigation is how gustatory signals are encoded by the nervous system. The principles of sensory coding from the retina to visual cortex were elucidated decades ago. We have a sound understanding of tonotopic and computational maps for the auditory system. Lateral inhibition and somatosensory receptive fields are well defined. Comparable insights into taste are lacking and we still do not understand how the brain distinguishes sweet, sour, salty, and so forth. If taste does not follow a simple labeled-line code, how are gustatory signals transmitted and deciphered? Ongoing studies include the possibility that taste is encoded in the time domain, i.e., by the frequency and pattern of action potentials in hindbrain and cortical neurons (Di Lorenzo et al., 2009; Miller and Katz, 2010). Other laboratories are exploring higher-order cortical processing via functional magnetic resonance imaging to address the interaction between taste detection, preference, and appetite regulation (Rolls, 2006; Small et al., 2007; Accolla and Carleton, 2008).

A critical chasm in our understanding of taste is how gustatory mechanisms are linked to mood, appetite, obesity, and satiety. The obvious link is that taste guides and to a large extent determines food selection, with salty, sweet, and fat tastes being the main actors. A fascinating link between appetite and moods is that serotonin-enhancing drugs, commonly used for treating mood disorders and depression, were shown to influence taste thresholds (Heath et al., 2006). Whether the mechanism of this action depends on the inhibitory action of 5-HT in taste buds remains to be determined, but the findings are intriguing (Kawai et al., 2000).

Cracks in the hard nut of appetite regulation are exposing a new dimension of taste—the impact of appetite-regulating hormones on peripheral gustatory sensory organs. A number of neuropeptide hormones activate hypothalamic and hindbrain circuits that regulate appetite. We are now learning that several of these same peptide hormones, including leptin, glucagon-like peptide, and oxytocin, modulate chemosensory transduction at the level of the taste bud. Circulating leptin, acting directly on taste receptor cells, reduces sweet responses measured in taste buds, in afferent nerves, and by behavioral tests (Kawai et al., 2000; Nakamura et al., 2008). Circulating oxytocin, another anorectic peptide, also acts on taste buds (Sinclair et al., 2010). Blood-delivered satiety peptides may be ideal candidates for integrating sensory and motivational drivers of appetite. Additional satiety peptides, including glucagon-like peptide-1, are synthesized within taste buds and act on taste cells or nerves (Shin et al., 2008). This research might provide avenues into therapeutic approaches for obesity, and at a minimum further help explain the seemingly insatiable human drive to consume calories.

Finally, another new direction for taste research is the presence of taste receptors and their downstream intracellular effectors in sensory cells of the gut (Rozengurt and Sternini, 2007; Kokrashvili et al., 2009a). The existence of these "taste" mechanisms in the gut is perhaps not surprising, given the importance of sensing the chemical nature of luminal contents at all points along the GI tract. However, the findings have generated new excitement in understanding how the gut participates in detecting and controlling appetite in general, and digestive processes in particular.

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