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Taste buds: cells, signals and synapses

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Abstract

The past decade has witnessed a consolidation and refinement of the extraordinary progress made in taste research. This Review describes recent advances in our understanding of taste receptors, taste buds, and the connections between taste buds and sensory afferent fibres. The article discusses new findings regarding the cellular mechanisms for detecting tastes, new data on the transmitters involved in taste processing and new studies that address longstanding arguments about taste coding.

Taste buds are the peripheral organs of gustation and are located mainly in the tongue epithelium, although they are also present elsewhere in the oral cavity. They sample the chemical makeup of foods and beverages for nutrient content, palatability and potential toxicity. The substantial diversity and redundancy of the molecular receptors for these compounds may reflect the importance of identifying nutrients and avoiding chemical threats from the environment. The molecular recognition of tastants, which occurs at the apical tips of taste bud cells, ultimately results in sensory perceptions (for example, sweet, salty, and so on) that guide appetite and trigger physiological processes for absorbing nutrients and adjusting metabolism. This Review discusses the proteins and pathways that taste buds use to detect stimuli, the communication and modulation that occur between their cells, and the nerve fibres that innervate taste buds, as well as the principles of the coding by which information is conveyed from the periphery to neurons in the CNS. Each of these areas has seen many new developments, controversies and clarifications in the past decade.

Chemosensory transduction

Taste buds are sensory end organs that are located in the oral epithelium (BOX 1). The receptors on the chemosensitive apical tips of taste bud cells confer specificity to gustatory stimuli. Taste receptors come in many types, including several classes of G protein-coupled receptors (GPCRs) and ion channels (FIG. 1). Some stimuli interact with receptors to generate second messengers, whereas in other instances, the taste stimulus itself is transported into the cytoplasm of taste bud cells and activates downstream events.

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Taste bud cells can be organized into three main types, in part according to their function. In general, bitter, sweet and umami stimuli are detected by type II cells[1–3], sour stimuli are detected by type III cells[4–6], and salty (NaCl) stimuli are detected by as-yet-undefined taste bud cells[7]. Below, we describe the mechanisms by which gustatory stimuli are transduced by taste buds. We remind readers that sweet and bitter, for example, are sensory perceptions; the compounds that elicit them are labelled with these same names as a shorthand in this Review, to which purists may object.

Sweet

Taste buds detect sugars (probably as an indication of carbohydrates) and other sweet stimuli using diverse mechanisms. The best-studied receptor for sweet stimuli is the heterodimer formed of two GPCRs: namely, taste receptor type 1 member 2 (T1R2) and T1R3. These subunits were identified by screening for mRNAs that are preferentially expressed in mouse taste buds[8] or by genetic linkage to *Sac*, which is a locus known to dictate sweet-taste sensitivity in mice[9–11]. When cultured cells are co-transfected with T1R2 and T1R3, they respond to sucrose, fructose, artificial sweeteners and some d-amino acids that elicit a sweet taste[12, 13].

T1R2 and T1R3 belong to family C of the GPCRs[14]. They each possess a long extracellular amino terminus that forms a venus flytrap module (VFM). T1R2 and T1R3 function as a heterodimer, and have multiple ligand-binding sites. Nevertheless, the purified extracellular domain alone of either T1R2 or T1R3 is capable of binding many sugars and sugar alcohols[15]. Modelling and experiments with chimeric and point-mutated T1R2 and T1R3 have demonstrated that sugars and dipeptide sweeteners (for example, aspartame) bind in the cleft of the VFM, albeit at slightly different positions[16–18]. Intensely sweet proteins (for example, monellin and brazzein) bind in the VFM and in a cysteine-rich domain that links the VFM to the transmembrane region[19, 20], and small-molecule sweeteners (for example, cyclamate) bind at residues in or near the transmembrane domains[16].

Mice that lack T1R2 or T1R3 have been reported to lose all behavioural sensitivity and neural responses to sugars and artificial sweeteners[21]. However, another group has reported that knocking out the gene that encodes T1R3 (*Tas1r3*) variably affects responses to sugars while eliminating the detection of artificial sweeteners[22]. This finding suggests that T1R3-independent mechanisms probably exist for the detection of sugars and other sweeteners[22, 23]. One postulated T1R3-independent mechanism involves glucose transporter type 4 (GLUT4) and sodium/glucose cotransporter 1 (SGLT1), which have been shown to transport glucose into sweet-sensing taste cells, leading to a transient elevation of intracellular ATP[24]. ATP that is generated by this pathway blocks ATP-inhibited K^+ channels (KATP channels) to depolarize the membrane[24]. Disaccharides such as sucrose are hydrolysed to hexoses and can then activate this pathway[25]. The involvement of a Na^+-dependent transporter — that is, SGLT1 — in transducing sugars offers a plausible explanation for the potentiation of sweet taste by Na^+ salts[26].

T1R3-independent pathways for transducing sugars may also trigger physiological reflexes independently of sweet-taste perception. Orally applied sugar has long been known to produce a small but marked elevation in plasma insulin levels within minutes, long before

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the sugar is absorbed in the gut. This cephalic-phase insulin release (CPIR) is documented in rodents and humans, and requires intact taste nerves[27–29]. CPIR requires vagal stimulation of the pancreas[29]. Insulin release from the pancreas may also be stimulated by glucagon-like peptide 1 (GLP1; also known as incretin), which is secreted by sweet-sensing taste bud cells[30, 31]. Sugar-induced CPIR persists in *Tas1r3*-knockout mice[32] and is mediated through the action of KATP channels[33]. Thus, at least two distinct and parallel sugar-sensing mechanisms seem to be initiated in taste buds: one that signals the perception of carbohydrate-rich foods (that is, sweet tastes, via T1R2–T1R3) and one that deploys a physiological reflex of insulin secretion (via a transporter).

Starch — which is a high-molecular-weight polymer of glucose — has long been considered to be tasteless to humans (but see REF.[34]). However, rodents show a strong appetitive preference for solutions containing smaller polymers such as Polycose[35]. Intriguingly, mice in which *Tas1r3* and *Tas1r2* have been knocked out can still detect Polycose[36, 37]. Given the nutritional importance of carbohydrates in most animals, the detection of sugars by glucose transporters and KATP channels may reflect a parallel mechanism for ensuring caloric sufficiency.

Umami

Some amino acids, notably glutamate and aspartate, have a savoury taste named umami. The prototypic stimulus for umami is monosodium glutamate (MSG). Glutamate is abundantly present in meat, fish, cheese and many vegetables. When 5′ nucleotides, such as 5′ inosine monophosphate (IMP), are present in small amounts alongside glutamate, there is a synergistic augmentation of umami taste[38].

Taste cells detect umami stimuli through multiple receptors. A sizeable amount of literature documents a role for T1R1–T1R3 heterodimers in transducing the umami taste[13, 21, 39]. An initial report using *Tas1r3*-knockout mice, mice that lack *Tas1r1* (which encodes T1R1) and double *Tas1r3;Tas1r1*-knockout mice claimed that T1R1–T1R3 heteromers were fully responsible for all umami taste detection[21]. However, studies using an independently generated *Tas1r3*-knockout line (see above) showed that the behavioural and neural responses of these mice to umami compounds (MSG and IMP) were nearly normal[22, 40]. Furthermore, a second line of mice in which *Tas1r1* was knocked out also demonstrated near-normal responses to umami compounds in taste bud cells and nerves; the only major change was that the nucleotide-mediated augmentation of umami taste was lost[41]. Thus, it seems that T1R1–T1R3 responds primarily to mixtures of MSG and nucleotides.

Umami taste receptors other than T1R1–T1R3 are also present in taste bud cells; these include N-terminal-truncated, taste-specific variants of the two metabotropic glutamate receptors mGluR4 (REFS[42, 43]) and mGluR1 (REF.[44]). Both of these receptors are activated by glutamate at concentrations that are found in foods[42, 44]. Nerve recordings from mice that lack *Grm4* (which encodes mGluR4) revealed decreased responses to glutamate and IMP, confirming that a fraction of the afferent nerve response to MSG in wild-type mice is attributable to mGluR4 (REF.[45]).

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Bitter

Bitter taste is stimulated by an enormous variety of compounds that have diverse chemical structures, from simple salts to large complex molecules, many of which are toxic. Bitter-taste receptors (T2Rs) are class A GPCRs, and have short N termini and ligand-binding sites in their transmembrane segments[46]. Unlike T1Rs, the T2Rs are generally considered to function as monomers, although recent evidence suggests that they may also form homodimers and heterodimers[47]. Many mammalian genomes (including the human genome) have 20 or more genes that encode T2Rs; by contrast, only three T1R-encoding genes have been identified in mammalian genomes. Subsets of T2Rs are co-expressed in any given bitter-sensing taste bud cell[48, 49]. T1Rs (which detect sweet and umami tastes) and T2Rs are expressed in a non-overlapping pattern[50], suggesting a separation of receptor cells that detect appetitive versus aversive stimuli.

Individual T2Rs in humans and rodents can be narrowly tuned to one or a very few bitter compounds, whereas others are broadly responsive to several bitter chemicals. The breadth of the receptive ranges of human T2Rs has been encyclopaedically documented in a thorough study of heterologously expressed taste receptors[51]. This study showed, for instance, that T2R3 responds to only a single compound (out of 94 different natural and synthetic compounds tested), whereas T2R14 responds to at least 33 compounds. Conversely, a single bitter compound often can activate multiple different T2Rs[51–54]. For example, quinine activates as many as nine different human T2Rs, whereas acetaminophen — an analgesic — stimulates just one human T2R[51]. This broad and overlapping range of ligand sensitivities of the T2Rs assures that this family of receptors responds to an enormous range of bitter-tasting chemicals (BOX 2). Presumably, this redundancy evolved to ensure the detection of potentially toxic (bitter-tasting) chemicals and thus prevent the consumption of harmful foods. An evolutionary note in this context is that orthologous receptors in mice and humans often are responsive to very different bitter tastants[54], which suggests that receptors have been reassigned to ecologically relevant compounds and that the gene family has been subjected to selective pressures[55]. Many T2Rs exhibit functional polymorphisms that result in varying abilities to taste particular compounds[56], and these polymorphisms may underlie differences in food preference[57] (BOX 3).

Effector pathways for sweet, umami and bitter taste receptors

In spite of their diversity, T1Rs and T2Rs converge on a common intracellular signalling pathway. These GPCRs all couple to heterotrimeric G proteins that include Gβ3 and Gγ13, as well as Gαgus (also known as gustducin), Gα14 and Gαi (REFS[58–60]). Gα subunits were originally proposed to activate cAMP signalling[61], but the current view is that they primarily function to regulate Gβγ subunits. cAMP also seems to have a longer-term role by maintaining signalling proteins in a responsive state through protein kinase A activation[62]. When T1Rs and T2Rs are activated by tastants, Gβγ dimers are released, which stimulates phospholipase Cβ2 to mobilize intracellular Ca^{2+} (REFS[1, 58]). Elevated cytosolic Ca^{2+} levels lead to the opening of transient receptor potential cation channel subfamily M member 5 (TRPM5), which is a cation-permeable channel that effectively depolarizes taste cells[63–65]. Interestingly, these same receptors and components of the same signalling pathways are also

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found in specialized cells in other tissues, where they may detect chemical stimuli without eliciting 'taste' per se (BOX 4).

Sour

The proximate stimulus for sour taste is intracellular acidification rather than extracellular protons[66]. Organic ('weak') acids, such as citric acid and acetic acid, are more potent stimuli of sour taste than are mineral ('strong') acids such as HCl. This is attributed to the greater membrane permeability of the undissociated organic acid molecule and the subsequent generation of protons in the cytoplasm. By contrast, mineral acids readily dissociate in the extracellular solution, but most cell membranes are relatively impermeable to protons. Thus, citric acid and acetic acid are more potent stimuli of sour taste than is HCl when tested at a similar pH. The taste bud cells that depolarize and produce Ca^{2+} responses to acids are the neuron-like type III cells[5, 67, 68].

Throughout the past two decades, numerous plasma membrane ion channels have been proposed as transducers for sour taste, including epithelial Na^+ channels (ENaCs)[69], hyperpolarization-activated cyclic nucleotide-gated channels[70] and acid-sensing ion channels (ASICs)[71]. More recently, two members of the TRP superfamily of ion channels — polycystic kidney disease protein 1-like 3 (PKD1L3) and PKD2L1 — were proposed as the major transducers of sour taste[4, 72]. However, all of these candidates have been ruled out as sour taste transducers either because they lacked biophysical characteristics that were consistent with sour-evoked responses in taste cells, or because mice in which the candidate receptor-encoding genes were knocked out retained all or most of their sensitivity to sour tastants[73, 74].

Confocal imaging of pH and Ca^{2+} has shown that organic acids permeate type III cells, acidify the cytoplasm and block leak K^+ channels to depolarize the cell membrane[67, 75]. These leak channels have recently been identified; specifically, type III cells express an inwardly rectifying K^+ channel, KIR2.1, which is inhibited by intracellular protons6. Extracellular protons, such as those contributed from mineral acids or from dissociated organic acids, pass through a proton conductance that seems to be concentrated to the apical tips of type III cells[68]. The molecular identity of the proton channel that is responsible for this proton movement remains to be established. The influx of protons through the channel generates a small depolarizing current, and furthermore, the accumulation of protons inside the cell contributes to the inhibition of KIR2.1 channels. The net result in both cases is depolarization of the type III sour-sensing cells such that they reach the threshold for action potential initiation[6].

Salty

The taste of NaCl is still somewhat of an enigma. Animals and humans readily consume NaCl below isotonic concentrations (that is, concentrations below approximately 150 mM). This appetite is presumably to ensure the adequate ingestion of an essential mineral. By contrast, higher concentrations of NaCl are normally aversive, which presumably reflects a survival mechanism that protects individuals against hypernatraemia and dehydration.

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It remains unclear exactly which taste bud cells transduce NaCl and what the transduction mechanisms are. Some of the key observations in this context are that, in rodents, amiloride, a diuretic, decreases the amplitude of responses to NaCl in afferent nerve recordings[76, 77] and reduces the behavioural response (licking) to NaCl solutions[77]. Yet, amiloride does not seem to change the perception of the saltiness of NaCl in humans[77, 78]. In rodents, amiloride affects neural responses mainly to NaCl; the effect on other salts is less consistent[77]. The dampening of NaCl taste by amiloride has long been interpreted as evidence for the essential role of the amiloride-sensitive Na^+ channel ENaC in salty taste[76, 79].

Fungiform taste bud cells loaded with a Ca^{2+} indicator have been reported to respond to apically applied NaCl[7]. When the gene encoding the obligatory α-subunit of ENaC was conditionally knocked out in taste cells, neural responses and the ability of mice to respond behaviourally to NaCl were lost[7]. These data confirmed earlier interpretations that ENaC is necessary for salty taste detection in rodents. However, no evidence has yet directly demonstrated that ENaC is the principal salt receptor in humans.

In a subsequent study, the authors reported that the signals for low (preferred) concentrations of NaCl originated in amiloride-sensitive taste bud cells, whereas high (aversive) NaCl concentrations were detected by completely separate amiloride-insensitive taste bud cells[80]. They further inferred that the two cell types transmitted their signals along separate afferent neurons. However, Ca^{2+} imaging subsequently showed that the amiloride sensitivity of afferent neurons was similar regardless of their NaCl sensitivity[81]; that is, high-NaCl versus low-NaCl sensitivity did not covary with amiloride sensitivity[81].

To date, the identity of the taste bud cells that sense NaCl is not known. Amiloride-sensitive Na^+ currents have been reported in taste bud cells that are neither type II or type III cells, based on their lack of voltage-gated currents[82]. By contrast, a report from another group demonstrated that the amiloride-blocked resting conductance was most prominent in cells that had the characteristics of type II cells[83]. Neither of these studies pinpointed the ENaC-mediated currents to cells that could be identified by type-specific molecular markers. Yet other reports assign amiloride-insensitive responses to NaCl to acid-sensing type III cells[80, 84]. This is an area ripe for clarification.

Fat

Dietary fats consist largely of triglycerides. Solid fats and oils differ in the length of the fatty acid chains of the triglyceride and the number of unsaturated positions. Most animals have a well-developed preference for fats. The sensations evoked by dietary fats most certainly include somatosensory components such as texture and viscosity. Whether fats stimulate a gustatory component remains debated. Rats lose their ability to detect and identify certain fats if the innervation of their taste buds is interrupted[85] which supports a role for taste buds in sensing fats. The principle argument against fat as a taste quality is that triglycerides have not been shown to stimulate taste cells. However, oral lipase activity in rodents rapidly and effectively digests fats into free fatty acids in the immediate environment of taste buds[86]. Fatty acids themselves are effective taste stimuli (see below). In humans also, oral lipase activity is detectable but only at low levels[87, 88], leaving its role in fat detection unresolved. There may not be a singular fat taste quality, as dietary free fatty acids evoke multiple

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orosensations — including ‘fatty’ and ‘irritating’ — depending on chain length and concentration[89].

One of the earliest studies on fat taste reported that certain polyunsaturated fatty acids act directly on K^+ channels, resulting in the prolonged depolarization of taste bud cells[90]. More recently, receptor-mediated mechanisms have been documented, including roles for a transporter for fats, CD36 (also known as platelet glycoprotein 4)[91, 92], and two GPCRs, GPR40 and GPR120 (also known as free fatty acid receptors 1 and 4, respectively)[93, 94]. CD36 was reported to be localized to the apical tips of some taste bud cells[92] and to elicit elevations in intracellular Ca^{2+} levels when stimulated by fatty acids[96]. How the transporter couples to Ca^{2+} signalling is not yet known. Intriguingly, oral stimulation of CD36 by certain fatty acids elevates pancreatic secretions[92] — which is suggestive of a ‘cephalic phase response’, preparing the gut for digesting lipids. GPR120 is expressed in a subset of rodent type II cells and, when activated, mobilizes Ca^{2+}, as is the case for T1R and T2R activation97. GPR120 seems to be distributed and function similarly in human taste buds[89]. In mice, knocking out the gene that encodes CD36, GPR40 or GPR120 results in partial deficits in fat taste[92, 94].

In short, fat taste is complex, and no particular transduction mechanism has been unambiguously identified. Indeed, several transducer proteins may interact to generate the taste of fat.

Aside from the basic taste qualities discussed above — sweet, bitter, salty, sour and perhaps fatty — additional tastes have been described (BOX 5).

Neurotransmitters and modulators

At least five neurotransmitters have been identified in taste buds. Their release and possible roles in taste have been examined in detail, and are discussed below. In addition, several peptides that function as hormones or neuromodulators interact with the taste system by influencing the sensitivity or the output of taste buds. As the topic of the role of peptides in taste has been reviewed recently[98], we focus here on small-molecule transmitters.

ATP

Early suggestions that ATP is a transmitter for taste buds were based on immunostaining for P2X purinoceptors in nerves associated with taste buds in rat tongues[99]. A role for this transmitter in taste signalling was validated in a study showing that sheets of lingual epithelium containing taste buds secreted ATP when stimulated with bitter tastants[100]. Furthermore, when the genes that encode the purinoceptors P2X2 and P2X3 were knocked out, mice became taste-blind to sweet, salty, bitter and umami[100].

Later studies showed, however, that in these knockout mice, the evoked release of ATP also was markedly diminished, somewhat weakening the argument that these receptors are the exclusive postsynaptic targets on sensory afferent fibres[101]. Nevertheless, most evidence supports the essential role of P2X2 and P2X3 as principal players in taste transmission. Experiments that used cellular biosensor cells to detect transmitter release have

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demonstrated the tastant-evoked release of ATP from individual type II cells[102, 103]. ATP release is greatly reinforced and amplified by autocrine feedback via the P2X and P2Y receptors expressed by type II cells[101, 104] (see below), which accounts for the loss of ATP secretion when the genes that encode P2X2 and P2X3 are knocked out.

Type II taste receptor cells secrete transmitters onto afferent fibres through an atypical, non-vesicular mechanism that involves large-pore membrane channels, which were initially proposed to include pannexin 1 (which is encoded by *Panx1*)[102] or connexins[103]. The identity of the ATP-release channel was subsequently revised to calcium homeostasis modulator protein 1 (CALHM1)105. A feature that made pannexin 1 channels particularly attractive as potential ATP-release channels was their gating by the combined action of depolarization and intracellular Ca^{2+} (REFS[102, 106]), both of which occur simultaneously in taste cells during tastant-induced stimulation. Conversely, a confounding feature of CALHM1 channels as the conduit for ATP release is their requirement for an unphysiologically low level of extracellular Ca^{2+} for gating[105, 107]. Nevertheless, the finding that *Panx1*-knockout mice showed continued secretion of ATP and taste afferent transmission[108, 109], combined with the observation that *Calhm1*-knockout mice exhibit taste deficits[105, 110], firmly swayed the balance towards CALHM1 channels as the ATP-release channels that function in taste cells.

The high concentration of intracellular ATP (in the millimolar range) drives efflux through CALHM1 channels when they are opened by taste-evoked action potentials[105]. Even in the absence of synaptic clefts between type II cells and afferent fibres, ATP secreted into the confined extracellular spaces reaches sufficient concentrations to stimulate P2X receptors on nearby afferent fibres[100]. Interestingly, large ‘atypical’ mitochondria are located directly below the plasma membrane of type II cells near sites where innervating afferent fibres pass in close apposition[111]. These mitochondria are optimally positioned as potential sources of presynaptic ATP for afferent transmission.

Mechanisms for removing extracellular ATP and thus terminating taste-evoked synaptic transmission include the degradation of ATP by the ectoATPase on the surface of type I cells[112, 113] and by an ectonucleotidase on type III cells[114]. The by-products of ATP breakdown, ADP and adenosine, contribute positive autocrine feedback by activating P2Y and A2 adenosine receptors, respectively, on type II cells[104, 114]. ATP also amplifies its own release by activating P2X receptors on type II cells[101, 104]. When this autocrine feedback is disrupted, an insufficient amount of ATP is secreted to activate nerves. ATP secreted from type II cells also acts as a paracrine stimulus for type III cells, leading to 5-hydroxytryptamine (5-HT; also known as serotonin) release from the latter cells[102] (see below).

5-HT

The first taste neurotransmitter for which taste-evoked release was demonstrated experimentally was 5-HT[115]. Studies using cellular biosensors identified type III cells as the source of stimulus-secreted 5-HT. This was consistent with the long-established finding that these cells synthesize 5-HT and store it in synaptic vesicles[116–118]. Several distinct stimuli, including KCl-induced depolarization and sour tastants, elicit 5-HT release from type III

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cells in a depolarization-dependent and Ca^{2+}-dependent manner[119]. Patch-clamp recordings from type III cells have demonstrated depolarization-induced vesicular exocytosis, presumably of the 5-HT-containing vesicles contained in these cells[120].

Type III taste bud cells also secrete 5-HT in response to the paracrine release of ATP from type II cells (see below). Curiously, 5-HT released from type III cells is mediated by two separate mechanisms[115] that involve either the mobilization of intracellular Ca^{2+} stores following ATP stimulation[104], or Ca^{2+} influx triggered by sour taste stimuli or KCl-induced depolarization[119, 120].

One function of 5-HT in taste buds seems to be to inhibit ATP secretion from type II cells[104] (but see REF.[121]), providing negative feedback to taste excitation. Synaptically released 5-HT also excites sensory afferent fibres at well-defined synapses[122, 123].

GABA

The inhibitory transmitter GABA is synthesized by, stored in and released from type III cells[119, 124, 125]. Correspondingly, type II taste cells express GABA type A receptors (GABAARs) and GABABRs receptors[125]. GABA seems to act within the taste bud to inhibit ATP release from type II cells[119]. Furthermore, sensory afferent neurons and their peripheral, taste bud-innervating processes express GABAARs[125]. Indeed, nearly every gustatory sensory neuron expresses GABAARs in addition to P2X2 and P2X3 receptors for the aforementioned purinergic signalling from taste bud cells[126]. Intriguingly, GABAARs seem to be limited to the neuronal soma and peripheral processes; the central processes of these neurons lack these receptors[126]. GABA inhibits the activation of gustatory ganglion neurons *in vitro*[127]. However, although it is inferred that GABA secreted in the periphery modulates afferent responses, this has not yet been demonstrated.

Acetylcholine and noradrenaline

In addition to secreting ATP, type II cells also secrete acetylcholine (ACh), as suggested by early findings that taste buds are rich in acetylcholinesterase[128, 129]. ACh release seems to function as an autocrine mechanism for increasing type II cell release of ATP, either by the selfsame type II cell or by the spread of ACh released from adjacent type II cells. Biosensor cell assays have also established that type III cells can uptake and re-release noradrenaline[117, 130]; the function of noradrenaline in taste remains unclear.

Cell–cell communication

A view of cell–cell interactions within taste buds has developed that suggests that signal processing in the peripheral organs of taste is more complex than was previously thought.

Sweet, bitter and umami compounds directly stimulate type II taste bud cells, and this is consistent with the expression patterns of the taste GPCRs for these compounds. The ATP that is released from type II cells during tastant-induced stimulation activates sensory afferent fibres, as described above, but ATP also excites adjacent type III cells via their P2Y receptors[102, 104]. Thus, in addition to being directly activated by acidic (sour) taste stimuli, type III cells also respond — albeit indirectly — to sweet, bitter and umami tastants[131, 132].

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The stimulation of type III cells by ATP induces them to secrete 5-HT and GABA, which in turn inhibit ATP release from type II cells. 5-HT and GABA provide negative feedback onto type II cells during tastant-induced activation[104, 119, 121, 133]. Details of how the release of 5-HT and GABA is balanced, what specific conditions stimulate 5-HT and/or GABA release, and the eventual impact of inhibitory transmitters on the taste afferent signal have yet to be explored.

Another form of cell–cell communication may exist between taste buds. The activation of one taste bud has been reported to inhibit surrounding taste buds, although the mechanism of inhibition was not determined in these studies[134–136]. Glutamate, presumably released from the collateral branches of afferent axons during tastant-induced stimulation, was recently shown to selectively activate type III cells[137, 138]. As the activation of type III cells induces the release of 5-HT and GABA, the glutamate-evoked release of inhibitory transmitters may explain the inhibition by axon collaterals[137]. However, species differences in axon branching and patterns of innervation[139] limit a clear elucidation of this inhibitory mechanism.

The autocrine, paracrine and synaptic circuits that are present in taste buds are detailed in REF.[140] and summarized in BOX 1.

Taste coding

How information from taste buds is transmitted to the CNS (specifically to neurons in the nucleus of the solitary tract) and, in particular, how signals discriminating sweet, sour, salty, bitter, umami and possibly other tastes are encoded are thorny questions. There has been more than 75 years of heated debate over these issues. At one extreme is the labelled-line coding model, which states that individual taste bud cells exclusively identify a unique taste quality (for example, sweet taste) and synapse with afferent fibres that are dedicated to that quality[141, 142]. Moreover, the central projections of the afferent neurons are ‘labelled’ by that same taste quality and synapse with dedicated hindbrain neurons that relay the information for that one quality to higher brain centres, thereby establishing a ‘labelled line’ of transmitted information.

An early suggestion of labelled-line coding in the periphery came from single-unit recordings in rodents, which showed that individual fibres respond best to one taste quality (for example, “NaCl-best”), although activity was also elicited by tastants of other qualities[143]. Studies on a number of other types of mammal have shown that sweet-responsive fibres are particularly well-tuned to sugars and artificial sweeteners[144].

The expression patterns of taste receptors in taste buds lend strong evidence for taste quality distinction at the level of taste cells. T2Rs, which detect bitter stimuli, are not found in cells that express T1Rs, which detect sweet or umami stimuli[12]. Moreover, sour-sensing cells are a separate cell type from both T1R-expressing and TR2-expressing cells[4, 5]. Furthermore, the genetic ablation of only type III cells results in the selective loss of sour taste, as observed both at the behavioural level and in afferent recordings[4]. In addition, the expression of a modified opioid receptor — receptor activated solely by a synthetic ligand (RASSL) — in T1R-expressing cells drives behavioural preference for a compound that normally has no

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taste: namely, the synthetic opioid spiradoline[21]. Conversely, the expression of RASSL in T2R-expressing cells resulted in an aversion to spiradoline[145]. The implication is that sweet and bitter 'labels' are resident in particular cells; activating the afferent fibres that innervate these cells would thus result in stereotypical responses, consistent with labelled-line coding.

An alternative model for how taste is encoded in the periphery states that information is transmitted by combinatorial activity in multiple peripheral afferent fibres[81, 146, 147] (FIG. 2). According to this model, ensembles of dissimilar afferent fibres are activated by a taste stimulus. The overall combination of fibres activated encodes the taste quality, such as sweet. Indeed, such combinatorial coding has long been established for colour vision and characterizes odour recognition in the olfactory system[148].

Strong evidence for the combinatorial coding of peripheral taste comes from several lines of experimentation. First, taste buds contain both narrowly tuned cells and more broadly responsive ones. Specifically, separate populations of type II cells respond mainly to a single taste quality (for example, sweet or bitter). By contrast, type III taste bud cells respond directly to sour stimuli and indirectly (via cell–cell communication) to multiple taste stimuli[131, 132]. Second, there are decades of electrophysiological recordings from individual sensory neurons that innervate taste buds in animals ranging from rodents to primates. Many of these recordings have revealed the existence of highly tuned neurons — which are also referred to as 'specialists' — that respond overwhelmingly only to stimuli of one taste quality[143, 144, 149–153]. However, these same recordings also reveal neurons — called 'generalists' — that respond to two or more different taste qualities. The relative proportions of such specialist and generalist neurons vary substantially depending on the species, the choice of stimuli presented and the concentration of the stimulus. Often, one taste stimulus is most efficacious for a given neuron (for example, "sucrose-best" (REF.[143])), but even that property is not always fixed. Specifically, increasing the concentration of tastant-containing solutions (that is, increasing the stimulus strength) converts seemingly narrowly tuned neurons into broadly responsive ones, and neurons with one best stimulus at low concentration acquire a different 'best stimulus' at higher concentrations[81]. These observations are inconsistent with the fixed, labelled-line model of taste coding.

A third possibility is that taste qualities are encoded by different temporal patterns of activity in gustatory neurons. Although temporal coding has been implicated in brainstem and cortical gustatory centres[154–157], there is no evidence that information in peripheral sensory neurons is encoded by spike timing. Indeed, an early study showed that stimulating human taste buds with a train of electrical pulses evoked a taste sensation that did not change when the stimulus rate was altered[158]. However, this study did not test different patterns of electrical stimulation.

Taste coding in central taste pathways is beyond the scope of this Review and has been comprehensively reviewed elsewhere[159–161]. It suffices to say, however, that the three models — labelled-line coding, combinatorial processing and temporal patterning — continue to be raised as explanations of how taste is encoded in higher brain centres, including the primary gustatory cortex.

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Conclusions

Until recently, many researchers thought that questions underlying the cellular and molecular mechanisms of the basic taste qualities had been settled. This Review explains that although we indeed understand many of the receptors and transmitters that are involved in detecting sweet, sour, salty, bitter and umami tastes, major gaps in our knowledge remain. Issues awaiting resolution include the molecular identity of additional signalling pathways for detecting umami and sweet tastes; the cells involved in detecting salty tastes; whether 'fatty' is a basic taste; the role of cell–cell communication in taste buds; and, more broadly, how distinct taste qualities are encoded in sensory afferent fibres and beyond following their initial detection in the taste bud.

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Glossary

Intracellular acidification

The increased concentration of cytosolic hydrogen ions, which corresponds to a decrease in cytoplasmic pH. Intracellular acidification can result from metabolic processes, the dissociation of organic (weak) acids, or the influx of protons through channels or transporters.

Taste coding

The computational system by which trains of action potentials in sensory cells convey information about the quality, concentration and other features of a sensory stimulus.

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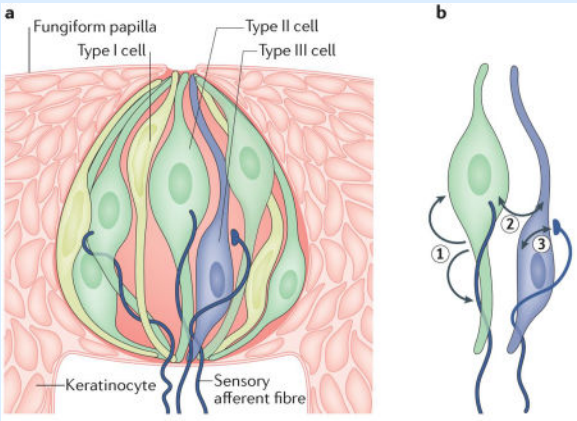
Box 1

Taste buds and their distinct cell types

Taste buds are clusters of columnar sensory cells that are embedded in the stratified epithelium of the tongue, palate and epiglottis. In mammals, each taste bud is a compact cluster of cells that resembles a garlic bulb, with 50–100 elongated cells extending from the base of the cluster to its apex and a few undifferentiated postmitotic cells at the base of the cluster. A classification scheme that integrates ultrastructural features and patterns of gene expression with cell function generally recognizes three cell types (in order of their relative abundance): type I, type II and type III cells (see the figure, part **a**; note that taste buds include many more cells than those that are depicted in the figure).



Type I cells comprise approximately half the total number of cells in a taste bud. They have narrow, irregularly shaped nuclei, are electron-dense and have wing-like cytoplasmic extensions that ensheath other taste bud cells[162, 163]. Type I cells seem to have glia-like functions. They express enzymes and transporters that are required to eliminate extracellular neurotransmitters[112, 113, 164] and ion channels that are associated with the redistribution and spatial buffering of K^+ (REF.[165]). Few other details are known about their function. Indeed, type I cells may be quite heterogeneous in terms of their gene expression patterns and their functions.

Approximately one-third of the cells in a taste bud are type II cells. These cells are larger in diameter than type I cells, have sizable spherical nuclei, and function as chemosensory receptors for sugars, amino acids and/or bitter stimuli as they express taste G protein-coupled receptors (GPCRs) and their downstream effectors. Most type II cells express one class of taste GPCR — namely, taste receptor type 1 (T1R) or T2R — and correspondingly respond only to one taste quality (for example, sweet or bitter, but not both)[131, 132]. It should be noted that T1R1, T1R2 and T1R3 are often co-expressed in taste bud cells, and, accordingly, responses to both sweet and umami stimuli can be detected in the same cells[41, 114]. The type II cells in a taste bud can differ in their expression of taste GPCRs such that each taste bud can respond to multiple taste stimuli.

Taste buds respond to more than one taste stimulus because they contain multiple type II cells of different specificities. Type III taste cells are the least numerous; they represent

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2–20% of the cells in a taste bud, and their incidence varies regionally in the oral epithelium. For instance, taste buds on the anterior tongue (fungiform taste buds) often contain no more than a single type III cell, whereas taste buds in the posterior tongue may contain as many as ten. These cells display slender profiles and oblong nuclei. They do not express taste GPCRs but do contain the machinery required to detect sour taste[4, 5, 68]. Type III cells have ultrastructurally recognizable synapses[162] with features such as clear and dense-cored vesicles, SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) proteins and densities in which the membranes of the taste cell oppose nerve fibres[166, 167]. By contrast, type II cells lack synaptic vesicles and communicate with closely apposed afferent fibres via non-vesicular transmitter release (see the main text).

In addition to the taste receptors, there are also receptors for ATP that mediate transmission from type II cells to nerves and autocrine feedback onto type II cells (1); receptors for ATP, serotonin and GABA that are responsible for cell–cell communication between type II and type III cells (2); and finally, receptors for serotonergic (feedforward) transmission and glutamatergic (feedback) transmission between type III cells and gustatory afferent fibres (3) (see the figure, part b).

Taste cells within taste buds are separated from the mucosal surface, blood supply and surrounding epithelium by a selective barrier that includes enzymatic components (extracellular ATPases), physical components (the zonula occludens) and molecular components (claudins, chondroitin sulfate and other glycosaminoglycans)[112, 168–171]. The barrier probably regulates which small molecules (for example, drugs, trophic factors, hormones and neuropeptides) can penetrate into the taste bud from the mucosal, serosal or vascular environments to influence the function of its constituent cells.

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Box 2

The discrimination of bitter tastes

Taste receptor type 2 (T2R) family members comprise a large group of taste G protein-coupled receptors (GPCRs) that detect bitter compounds; there are more than 40 T2R family members in rodents and 25 functional genes in humans. When the family was first described, T2Rs were reported to be expressed in an all-or-none manner in individual cells[50] or in a more combinatorial pattern[48]. If all T2Rs are expressed together in every bitter-sensing cell, the implication is that bitter is a homogeneous, singular taste quality[50]. Alternatively, if bitter-sensing cells express various combinations of T2Rs, it might be possible to discriminate bitter compounds[48].

Evidence has accumulated for both of these possibilities. Ca imaging of mouse taste buds and single-unit recordings from peripheral axons in rats have revealed that taste bud cells and neurons do in fact discriminate among several bitter-tasting compounds, with some responding to denatonium, others responding to quinine or cycloheximide, and yet others responding to two or more of these compounds[172, 173].

Recent studies that have systematically used numerous probe combinations on human taste buds have shown that chemosensory taste bud cells co-express overlapping subsets of 4–11 T2Rs and not the entire family[49]. In principle, this variation in co-expression could form the basis for the neural and perceptual discrimination of various bitter compounds. However, it is currently not known whether each T2R is expressed in a predictable combination with others or is expressed randomly. The former may be a prerequisite for discrimination. Although central neurons have been shown in some instances to discriminate among bitter compounds, this may involve additional receptor mechanisms and pathways[157, 174, 175]. Whether animals and humans are capable of behaviourally distinguishing bitter-tasting compounds is unresolved, and there is evidence both for[175] and against[176, 177] the discrimination of such compounds.

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Box 3

Brussels sprouts and broccoli: the genetics of taste preference

Variation in the genes that encode taste receptors probably generates different taste sensitivities among individuals. A well-known example involves the taste of phenylthiocarbamide (PTC) or related compounds. Individuals find PTC extremely bitter, moderately bitter or nearly tasteless (that is, they cannot detect the presence of PTC). These phenotypes were first reported nearly a century ago as an example of simple Mendelian inheritance with a dominant taster allele and a recessive non-taster allele[178]. The locus (TAS2R38, which encodes taste receptor type 2 member 38 (T2R38)) and underlying alleles were only recently identified[179]. Genetic analyses of human populations in Africa, Asia and Europe suggest that PTC-taster and non-taster alleles of TAS2R38 have been maintained by natural selection across more than 100,000 years of human evolution[180]. Similarly, an allele of the human gene TAS2R16 — which confers sensitivity to several β-glucopyranosides found in nature (for example, those in bitter almonds, bearberry and manioc) — has been subjected to positive selection pressure across human evolution[181, 182].

The PTC-taster allele of TAS2R38 encodes a receptor that detects a range of natural bitter compounds, some of which are toxic and others of which are beneficial. This finding supports the interpretation that both alleles are preserved in human populations on the basis of varied human diets and environments. For instance, heterozygous individuals find anthocyanin-containing cruciferous vegetables (such as Brussels sprouts and broccoli) less bitter than do those who inherited two PTC-taster alleles. Consequently, homozygous ‘tasters’ tend to reject these vegetables and may thus avoid the hypothyroidism that results from consuming large quantities of anthocyanin compounds when dietary iodine is deficient. Curiously, polymorphisms in some human T2R-encoding genes are associated with variation in the perceived bitterness of ethanol and other stimuli that are usually considered to activate trigeminal fibres rather than taste buds[183].

The anticancer benefit of phytochemicals present in cruciferous vegetables has motivated researchers to investigate whether there might be a relationship between certain bitter-taste receptor-encoding alleles, diet selection, and the incidence of colorectal cancer and other cancers. Most studies have failed to find an association between cancer incidence and polymorphisms in TAS2R14 (REF.[184]), TAS2R16 and TAS2R50 (REF.[185]). However, for TAS2R38, one laboratory has reported an association between a particular TAS2R38 haplotype and colorectal cancer risk[186], although another group failed to detect such an association[185].

The human T1R-encoding genes (which encode sweet or umami receptors) show great variability across human populations[187]. However, there are relatively few reports on taste phenotypes that are directly associated with these genetic alterations. A polymorphism in a non-coding region upstream of TAS1R3 was associated with a greater perceived intensity of sweetness that apparently resulted from increased transcription[188]. At least one polymorphism of TAS1R2 was reported to be associated with the increased

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intake of carbohydrates and elevated blood triglyceride levels in certain populations[189, 190]. Polymorphisms in TAS1R2 and TAS1R3 have also been associated with the risk of dental caries in children[191]. Furthermore, the ability of individuals to detect umami varies across populations and was shown to be associated with variation in TAS1R3 (REF.[192]).

Although genotype–phenotype associations are becoming apparent, functional studies on the receptors expressed by identified variants have yet to provide a molecular basis for the many observed variations in human taste and diet. Indeed, although taste receptor genetics may play a part in food selection, additional factors influence the complex human behaviours involved in this process.

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Box 4

Extraoral taste receptors

Taste G protein-coupled receptors (GPCRs) are not limited to the oral cavity or to sensing ingested foods and beverages. Instead, members of the large taste receptor type 2 (T2R) family, and the smaller T1R family, are found in several tissues and organs throughout the body[95, 193, 194] (see the table). The function of many of these extraoral taste GPCRs remains incompletely explored.

Extraoral taste receptors that have been studied the most extensively and for which we have a better understanding of function include those in the gut and airways. Elegant studies have described a functional role for T2Rs (bitter-taste receptors) and their downstream signalling partners in the ciliated cells of the airway epithelium[195, 196]. These studies showed that bitter compounds elicit the secretion of bactericidal nitric oxide and stimulate ciliary beating, promoting the clearance of bacteria and noxious compounds from the airways. One particular bitter-taste receptor that is localized to airway epithelium, T2R38 (which is encoded by TAS2R38), is activated by acyl-homoserine lactone, which is a quorum-sensing molecule that is secreted by Gram-negative bacteria. Polymorphisms in TAS2R38 are linked to susceptibility to respiratory and chronic rhinosinusitis in humans, which emphasizes the importance of this bitter-taste receptor in the upper airways[197, 198].

The nasal respiratory epithelium also includes another type of cell that expresses T2R: solitary chemosensory cells (SCCs). These chemosensory cells make synaptic contact with and release acetylcholine onto trigeminal sensory afferent fibres, thereby initiating a protective apnoea reflex[199, 200]. T2Rs on SCCs respond to quorum-sensing molecules and other bacterial secretions[196, 201]. The resulting Ca^{2+} signal seems to spread via gap junctions to surrounding respiratory epithelial cells, triggering an innate immune response that includes the secretion of antibacterial peptides[198].

Tissue	Taste GPCRs	Refs
Airway ciliated cells	T2Rs	195
Airway smooth muscle	T2Rs	207
Airway SCCs	T1Rs and T2Rs	194, 197
Brain: multiple regions	T1Rs and T2Rs	208, 209
Choroid plexus	T1Rs and T2Rs	210
Heart	T1Rs and T2Rs	211
Intestine	T1Rs and T2Rs	202, 204, 212
Keratinocytes	T2Rs	213
Kidney	T1Rs	214
Liver: bile ducts	T1Rs	215
Leukocytes	T1Rs and T2Rs	214, 216, 217
Pancreatic islets of Langerhans	T1Rs	218
Stomach	T2Rs	202

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Tissue	Taste GPCRs	Refs
Testis	T1Rs and T2Rs	214, 219, 220
Thyroid gland	T2Rs	221

It is intriguing that the same SCCs that express bitter-taste receptors that sense microbial secretions also have T1R sweet-taste receptors[198]. Glucose in the mucus is thought to be the stimulus for these receptors. Downstream effectors of the T1Rs tonically inhibit the T2R-mediated pathway in the same SCC. A high titre of bacteria in the airway mucus lowers glucose levels, releasing the T2R pathway from inhibition and promoting the antibacterial response. High glucose levels in the airway mucus of patients with diabetes may keep this protective pathway chronically suppressed[198].

T1Rs and T2Rs are also expressed in the gastric a quantitative analysis of expression levels and cell types using a knock-in fluorescent reporter demonstrated that only a very limited number of T2Rs may be expressed. Moreover, the T2Rs are not expressed in enteroendocrine cells, as was originally suggested[202, 203], but in goblet cells mechanisms[204]. Individual cells express some but not all components of the canonical taste signalling cascade[205]. The implication of this is that ingested nutrients and non-nutrient chemicals (such as glucose, peptides, amino acids, bitter compounds, fats and, possibly, the fermentation products of gut microbiota) stimulate taste receptors on gut cells to elicit various defence mechanisms and/or the secretion of appetite-regulating hormones[98, 203, 204]. Chemicals in the gastrointestinal lumen may also provoke SCCs to release transmitters — possibly acetylcholine[206] — that act in a paracrine manner on neighbouring enteroendocrine cells.

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Box 5

Less-studied tastes

Aside from the well-studied taste qualities (sweet, bitter, umami, sour and salty), food evokes additional sensory perceptions. One such sensation is chemesthesis. The pungency of chilli peppers, ginger, horseradish and black peppers is elicited by several unrelated compounds, including the vanilloids capsaicin and zingerone, the organosulfur compound allyl isothiocyanate, and the alkaloid piperine, respectively. These compounds are known to directly activate transient receptor potential cation channels (TRPs) — including TRPV1 and TRPA1 (REFS[222–225]) — that are expressed in nociceptors, causing irritation and/or pain. Hence, the pungency of peppers has been assumed to represent the activation of trigeminal nociceptors in the oral epithelium, which makes pungency not a taste modality per se (for example, see REF.[226]). However, subsets of neurons in the gustatory sensory ganglia have also been reported to express TRPA1 and TRPV1 (REF.[227]), and to display capsaicin-activated cation currents[228]. Thus, it remains to be established whether pungency is a specialized perception that originates solely from oral somatosensory (trigeminal) neurons or whether there is a genuine taste component as well. Trigeminal afferents — many of which terminate in close proximity to, if not actually within, taste buds — might release peptides that influence taste cell sensitivity, such as substance P or calcitonin gene-related peptide (CGRP)[229–233]. Another intriguing possibility is that capsaicin and other pungent stimuli activate keratinocytes, which then secrete neuroactive compounds to stimulate trigeminal or gustatory sensory afferent fibres, or both[234, 235].

A less tangible food-related sensation that was reported more recently is ‘kokumi’, which is described as thickness, longevity and mouthfeel (REF.[236]). Glutathione, and related dipeptides and tripeptides, are the principal kokumi stimuli. On their own they are nearly tasteless, but, when they are combined with sucrose, NaCl, monosodium glutamate or more complex solutions (for example, broth), these compounds elicit kokumi sensations without altering the primary taste (for example, sweet and umami)[237, 238]. Extracellular Ca^{2+}-sensing receptor (CaSR) — a G protein-coupled receptor that was originally identified in the parathyroid glands and is a key player in the body’s Ca^{2+} homeostasis — is expressed in subsets of taste bud cells and is a possible transducer for kokumi stimuli[239]. CaSR is reported to be allosterically modulated by sucrose and several other natural and synthetic sweeteners[240], and this modulation may account for the interaction between kokumi compounds and other taste stimuli.

Another little-studied aspect of taste is the ability to detect certain nutrients that are deficient in the diet. For instance, humans normally report that Ca^{2+} salts have an unpleasant taste that includes bitterness and sourness[241], and rodents show little taste preference for Ca^{2+} salts[242]. However, rodents greatly increase their intake of solutions containing Ca^{2+} salts if their diet is deficient in Ca^{2+} (REF.[242]). Curiously, Ca^{2+} appetite in mice[243] and humans[244] is associated with taste receptor type 1 member 3 (T1R3), which underlies sweet and umami tastes, rather than with CaSR. It remains unclear whether Ca^{2+} produces a consciously perceived taste that drives appetite.

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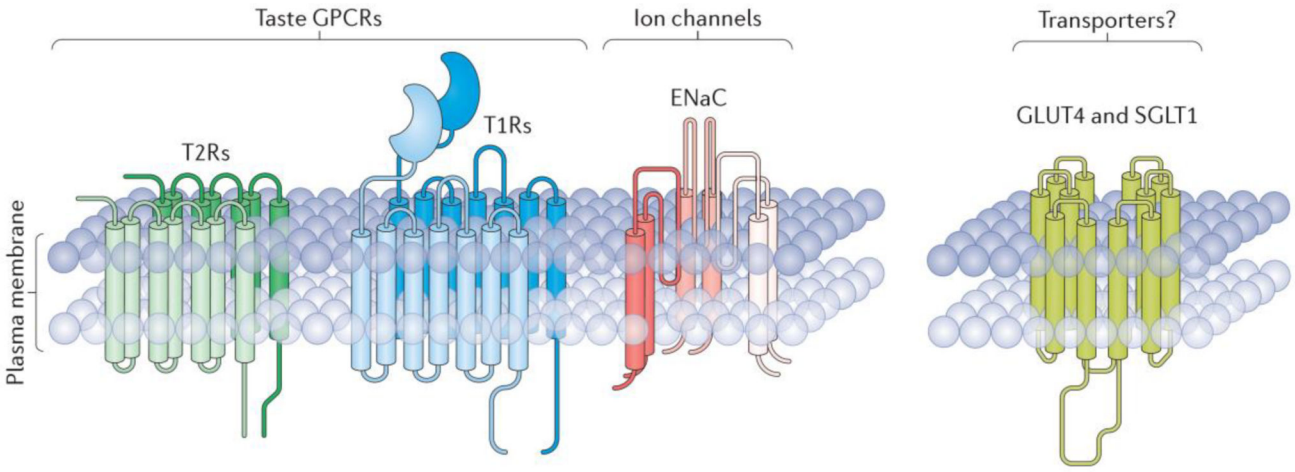

Figure 1. Membrane proteins that transduce taste

Type 2 taste receptors (T2Rs; bitter-taste receptors) are G protein-coupled receptors (GPCRs) that have short amino termini and may function as monomers (not shown) or dimers. T1Rs (sweet-taste and umami receptors) are also GPCRs, but they have long N termini that contain bilobed (venus flytrap) domains and function as dimers that use T1R3 as an obligate subunit. T1R1–T1R3 is an umami receptor, and T1R2–T1R3 is a sweet-taste receptor. All these taste GPCRs use a common transduction pathway that includes a Gβγ-activated phospholipase C (PLCβ2) and transient receptor potential cation channel subfamily M member 5 (TRPM5). The epithelial Na channel (ENaC) has three subunits and is thought to transduce salty taste in rodents. Glucose transporter type 4 (GLUT4) — which has 12 membrane-spanning segments — transports glucose by facilitative diffusion, whereas sodium/glucose cotransporter 1 (SGLT1) is Na dependent. One or both of these transporters are hypothesized to be part of an alternative glucose-sensing pathway that is similar to the one used in pancreatic β cells.

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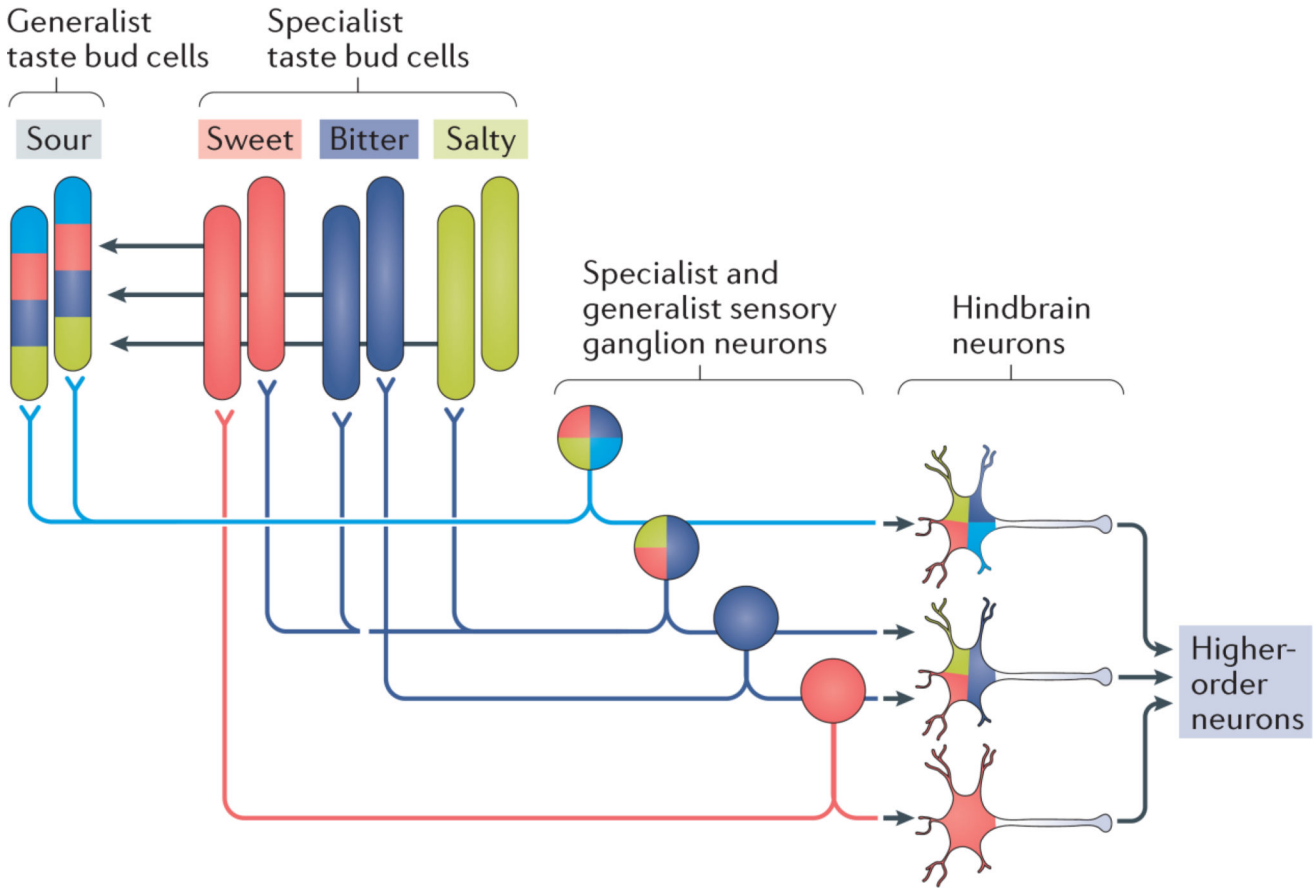

Figure 2. The combinatorial model of taste coding

Individual type II taste bud cells are mostly tuned to one taste quality (for example, bitter, sweet or salty): that is, they are 'specialists' (umami has been omitted for clarity). The type III cells sense sour tastes and also respond secondarily to other taste stimuli via cell-to-cell (paracrine) communication within the taste bud (represented by the arrows between the taste bud cells). Thus, type III cells can be termed 'generalists'. Some afferent ganglion neurons receive input from taste cells that respond to a single taste quality and hence would be specialist neurons. Other afferent ganglion neurons receive input from many taste cells or from type III cells and thus are multiply sensitive 'generalist' neurons. Moving to the CNS, sensory ganglion cells converge on hindbrain neurons in the nucleus of the solitary tract.