Taste Receptor Genes

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gustatory, sweet, bitter, umami, salty, sour

Abstract

In the past several years, tremendous progress has been achieved with the discovery and characterization of vertebrate taste receptors from the T1R and T2R families, which are involved in recognition of bitter, sweet, and umami taste stimuli. Individual differences in taste, at least in some cases, can be attributed to allelic variants of the T1R and T2R genes. Progress with understanding how T1R and T2R receptors interact with taste stimuli and with identifying their patterns of expression in taste cells sheds light on coding of taste information by the nervous system. Candidate mechanisms for detection of salts, acids, fat, complex carbohydrates, and water have also been proposed, but further studies are needed to prove their identity.

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INTRODUCTION

The major focus of this review is on the mammalian taste receptors from the T1R and T2R families. We also briefly discuss other candidate taste receptors in mammals.

Taste System

In the common language, the word "taste" is often used to describe sensations arising from the oral cavity. However, the biological definition of taste, or gustation, is narrower and includes only sensations mediated by a specialized anatomically and physiologically defined chemosensory gustatory system. Along with taste sensations, food usually simultaneously evokes other sensations, e.g., odor, touch, temperature, and irritation. Although it is not always easy to separate all these sensations perceptually, the nongustatory components are sensed by different systems, olfaction and somatosensation.

The gustatory system in mammals includes taste receptor cells (TRCs) organized in taste buds located within gustatory papillae. Most of the taste papillae belong to three types—fungiform, foliate, and vallate—and are located in the tongue. There is also a substantial number of nonlingual taste papillae in the palate, oropharynx, larynx, epiglottis, and the upper esophagus. Apical ends of the TRCs are exposed to the oral cavity and interact with taste stimuli, usually water-soluble chemicals. This interaction generates signals that are transmitted to the brain via branches of three cranial nerves, VII (facial), IX (glossopharyngeal), and X (vagus). One branch of the VII nerve, the chorda tympani nerve, sends fibers to the anterior part of the tongue including fungiform papillae and possibly to the anterior portion of the foliate papillae. The other branch of the VII nerve, the greater petrosal nerve, sends fibers to the taste buds on the soft palate. Axons of the glossopharyngeal nerve innervate vallate and foliate papillae, and possibly taste buds in the pharynx. Axons of the vagus nerve innervate taste buds in the epiglottis, larynx, and the upper esophagus

(170). These first-order ganglionic neurons terminate in the rostral part of nucleus of the solitary tract in the medulla. The upper-order projections from the nucleus of the solitary tract include parabrachial nucleus, thalamic taste area, insular-opecular (primary) taste cortex, caudolateral orbitofrontal (secondary) cortical taste area, amygdala, hypothalamus, and basal ganglia (144). This wide representation of taste information in the brain probably serves necessary to integrate it with interoceptive (hunger, satiety, specialized appetites) and exteroceptive (vision, olfaction, somatosensation) signals and to generate behavioral responses to taste stimuli. Central taste processing results in perception of several different aspects of taste: quality, intensity, hedonics (pleasantness or unpleasantness), location, and persistence.

Nutrition, Taste Reception, and Taste Receptors

The survival of all animals depends on consumption of nutrients. However, sources of nutrients often also contain toxic substances. Taste helps animals to decide whether a food is beneficial for them and should be consumed or whether it is dangerous for them and should be rejected. Probably, taste evolved to insure animals choose food appropriate for body needs.

The current consensus is that human taste sensations can be divided into five qualities: bitter, sour, salty, sweet, and umami (savory; the prototypical stimulus being the amino acid glutamate). Aversive bitter taste often indicates presence of toxins in food. Bitter and sour tastes may also signal spoiled food. The main salty taste stimuli are sodium salts, but some nonsodium salts also have a salty taste component. This suggests that salty taste signals the presence of either sodium or minerals in general. For some species, consummatory responses to salty taste stimuli differ widely between sodium-replete and -deplete animals. Concentrated salt solutions, which are aversive to sodium- or mineral-replete animals, can be palatable to animals with depletion. The most common natural sweet taste stimuli are sugars, which indicate the presence of carbohydrates in food. The most common umami taste stimulus is L-glutamate, which may indicate the presence of protein. Other important nutrients include lipids, calcium, and water, but the existence of taste qualities corresponding to them is debatable.

TRC: taste receptor cell

GPCR: G protein–coupled receptor

The existence of several different taste qualities implies that each taste quality has a specific coding mechanism mediated by specialized taste receptors. Current data support this hypothesis. Reception of taste qualities that humans describe as sweet, umami, and bitter involves proteins from the T1R and T2R families. Candidate receptors have been proposed for salty and sour tastes.

Traditionally, human sensations are used to describe the main five taste qualities. Although there are many studies showing that the mechanisms underlying perception of particular taste qualities are similar in human and nonhuman animals, applying terms for human sensations to nonhuman animals should be used with caution. It is more accurate to describe taste quality perception by nonhuman animals using chemical names of taste stimuli (e.g., sodium taste, or sucroselike taste), but for brevity we use in this review human descriptors for taste qualities.

What Are Taste Receptors?

Taste receptors function as chemoreceptors that interact with taste stimuli, or ligands, to initiate an afferent signal transmitted to the brain, which results in taste perception. Because many taste ligands do not easily permeate cell membranes, taste receptors are believed to be a part of the TRC membranes. Consistent with this belief, T1R and T2R receptors belong to a superfamily of G protein–coupled receptors (GPCRs) with characteristic seven domains spanning the plasma membrane. However, some other taste stimuli can penetrate cell membranes; these

include sodium, protons, and some bitter and sweet compounds. These compounds may interact with intracellular targets to activate TRC, and therefore the definition of what would be a taste receptor for such ligands is less clear.

Although a number of proteins have been suggested to function as taste receptors, not all of them have been unanimously accepted as such. We believe that to prove that a molecule functions as a taste receptor, several criteria must be met: (*a*) the molecular identity of the candidate receptor should be established, (*b*) its expression in TRCs should be confirmed, (*c*) appropriate ligands should be identified, and (*d*) changes in taste function resulting from changes in the taste receptor should be demonstrated.

Nomenclature and Classification of Taste Receptor Genes and Proteins

Publications on taste receptors have a number of discrepancies in naming genes and proteins [e.g., see **Supplemental Tables 1** and **2** (for all Supplemental Material, follow the Supplemental Material link from the Annual Reviews home page at **http://www.annualreviews.org**)]. This creates difficulties in comparing descriptions of the same gene that has different names in different publications. This situation is also common with other types of genes and may become especially confusing with large gene families present in multiple species, such as taste receptor genes. This problem resulted in attempts to unify gene and protein nomenclature (157).

The confusion with identification of taste receptor genes and proteins underscores the importance of following nomenclature rules. Guidelines for human, mouse, and rat gene nomenclature are accessible on the Internet (3, 5). For the two best-characterized families of taste receptors, T1R and T2R, standard gene names follow the following description: "taste receptor, type 1, member 1" (with corresponding type and member numbers). A corresponding gene symbol abbreviates this name to *Tas1r1* (in mouse or rat) or *TAS1R1* (in human); a corresponding protein symbol is T1R1 (uppercase letters and not italicized). For brevity, and especially when we refer to both human (*TAS . . . R*) and rodent (*Tas . . . r*) genes, we describe them as T . . . R genes. Besides differences in symbol letters (upper- or lowercase), human and mouse T2R genes can also be distinguished by member number: The human genes have member numbers smaller than 100 (*TAS2R1–TAS2R65*), whereas the mouse genes have member numbers higher than 100 (*Tas2r102–Tas2r146*). Genes and proteins of other species can be distinguished by adding a lowercase letter indicating species, e.g., *rTas2r123* for rat. Lists of human and mouse taste receptor genes, including their names, symbols, and synonyms, can be found in **Supplemental Tables 1** and **2**, and can also be found in the human (2) and mouse (4) genome databases. A compilation of human and mouse T2R gene symbols, alternative symbols, and GenBank accession numbers is published in (7). An ultimate identifier of a gene is its nucleotide sequence, which should be used if gene identity is not certain.

Several classification systems have been proposed for the GPCR superfamily. One of the most frequently used includes GPCRs of different vertebrate and invertebrate species and groups them into six classes (clans): A, B, C, D, E, and F (1). According to this classification, T1Rs belong to class C (metabotropic glutamate/pheromone) GPCRs. T2Rs are described either as a separate putative family (1) or as distantly related to class A (rhodopsinlike) GPCRs (6). More recently, the GRAFTS (glutamate-rhodopsin-adhesion-frizzled/taste2-secretin) classification system was developed based on phylogenetic analyses of transmembrane parts of human GPCRs (58). According to this classification, T1Rs belong to the glutamate family. T2Rs form a distinct cluster within the frizzled/taste2 family; the second cluster of this family includes the frizzled receptors involved in cell proliferation and development.

T1R RECEPTORS

Discovery

The discovery of three mammalian T1R receptors resulted from two converging lines of studies. The first line was related to identification of a genetic locus that affects saccharin preference in mice (the *Sac* locus). In 1974, using long-term two-bottle tests, Fuller (60) showed that differences in saccharin preferences between the C57BL/6 and DBA/2 inbred strains largely depend on a single locus, *Sac*, with a dominant Sac^b allele present in the C57BL/6 strain that was associated with higher saccharin preference and a recessive Sac^d allele present in the DBA/2 strain that was associated with lower saccharin preference. Subsequent studies confirmed this finding in the BXD recombinant inbred strains, and in crosses between the C57BL/6 and DBA/2 and between the C57BL/6 and 129 strains (16, 23, 26, 113, 115, 133). In addition to sweetener preferences, the *Sac* genotype influenced the afferent responses of gustatory nerves to sweeteners (16, 98), which indicated that the *Sac* gene is involved in peripheral taste transduction and may encode a sweet taste receptor. The *Sac* locus has been mapped to the subtelomeric region of mouse chromosome 4 (16, 26, 115, 133).

The second line of studies stemmed from analyses of a taste-bud-enriched cDNA library (72), which resulted in a discovery of two putative G protein–coupled taste receptors, T1R1 and T1R2 (71). Localization of the *Tas1r1* gene in the distal part of mouse chromosome 4, near the *Sac* locus, suggested that *Tas1r1* and *Sac* were identical. However, a high-resolution genetic mapping study rejected this possibility by showing distinct locations for *Tas1r1* and *Sac* (98). A positional cloning study at the Monell Chemical Senses Center has shown that the *Sac* locus corresponds to a novel gene, *Tas1r3*, which is the third member of the *Tas1r* family (14, 97, 137). These studies restricted the genomic position of the *Sac* locus to a critical interval not exceeding 194 kb and identified genes within this region. One of these genes, *Tas1r3*, was the most likely candidate for the *Sac* locus based on the effects of the *Sac* genotype on peripheral sweet taste responsiveness (16, 98) and the involvement of a G protein–coupled mechanism in sweet taste transduction (171). *Tas1r3* sequence variants were associated with sweetener preference phenotypes in genealogically diverse mouse strains (14, 137). Substitution of *Tas1r3* alleles in congenic mice resulted in phenotypical changes attributed to the *Sac* locus (14). These data provided evidence for the identity of *Sac* and *Tas1r3* and for the role of the T1R3 receptor in sweet taste.

Several other studies provided additional evidence that *Sac* and *Tas1r3* are identical:

1. A phenotype rescue transgenic experiment, in which a genomic clone containing the *Tas1r3* gene from the C57BL/6 mouse strain with a dominant *Sac* allele determining higher sweetener preference was incorporated in the genome of mice carrying a recessive *Sac* allele (from the 129X1/Sv strain) determining lower sweetener preference. The transgenic mice had higher taste preferences for sucrose and saccharin (but not for nonsweet taste solutions) compared with the 129X1/Sv mice (127).
2. Genetically engineered mice lacking the *Tas1r3* gene had diminished or abolished taste responses to sweeteners (46, 179).
3. Cells with heterologously expressed T1R2 + T1R3 proteins responded to sucrose and saccharin more strongly when the C57BL/6 *Tas1r3* allele was used compared with cell responses when 129X1/Sv *Tas1r3* allele was used (126).
4. An in vitro study (130) has shown that binding of several sweeteners to the extracellular N-terminal domain of the T1R3 protein was reduced when isoleucine at position 60 [a predicted sweetener-sensitive allele of the *Sac*/*Tas1r3* gene (137)] was substituted

to threonine (a predicted hyposensitive allele of the *Sac/Tas1r3* gene).

Additional evidence that the three T1R proteins function as taste receptors included the demonstration that: (*a*) T1Rs are expressed in taste receptor cells (46, 71, 86, 91, 92, 99, 101, 107, 120, 123, 127, 137, 147); (*b*) cell cultures with heterologously expressed T1Rs respond to taste stimuli (100, 126, 127, 179); and (*c*) targeted mutations of the *Tas1r* genes affect taste responses of the genetically engineered mice (46, 179).

Genomic Organization

The three mouse *Tas1r* genes are located in the distal chromosome 4 in the order *Tas1r2* (70.0 cM or 139 Mb, NCBI Build 36)—*Tas1r1* (81.5 cM or 151 Mb)—*Tas1r3* (83.0 cM or 155 Mb). Their human orthologs reside in a region of conserved synteny in the short arm of human chromosome 1 in the same order: *TAS1R2* (1p36.13)—*TAS1R1* (1p36.23)—*TAS1R3* (1p36.33) (see **Supplemental Figure 1**).

The mouse *Tas1r* genes contain six coding exons (**Supplemental Figure 2**) and are translated into 842–858-amino acid proteins. The T1R proteins (**Figure 1**) have a predicted secondary structure that includes seven transmembrane helices forming a heptahelical domain and a large extracellular N-terminus composed of a Venus flytrap module and a cysteine-rich domain connected to the heptahelical domain (134). There is evidence for alternative splicing of the T1R1 (**Supplemental Figure 3**), T1R2 (123), and T1R3 (92, X. Li and D. Reed, unpublished data) genes.

Tissue Expression

The main sites of expression of the T1R genes are TRC of the taste buds. In mice, rats, humans, pigs, and cats, the T1R3 gene is expressed in all types of taste buds (46, 91, 92, 99, 107, 120, 123, 127, 137, 147). Initial studies have shown that in mice and rats, the T1R1

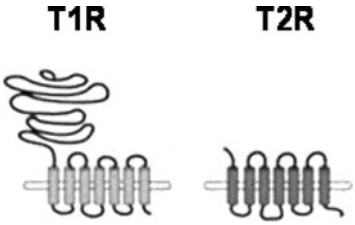

Figure 1

Conformation of T1R and T2R proteins. Both T1R and T2R proteins are predicted to have seven transmembrane domains. The T1R proteins consist of ~850 amino acids and have a large extracellular N-terminus. The T2R proteins consist of ~300–330 amino acids and have a short extracellular N-terminus.

gene is predominantly expressed in the fungiform and palate taste buds, is expressed in a smaller percentage of the foliate taste buds, and is rarely expressed in the circumvallate taste buds. The T1R2 gene is predominantly expressed in the circumvallate and foliate taste buds, is expressed in a smaller percentage of the palate taste buds, and is rarely expressed in the fungiform taste buds (71, 91, 123, 127). T1R1 and T1R2 are rarely coexpressed in the same TRC (71, 127). The T1R genes are not coexpressed with the T2R genes (127). In mice and rats, there are three main patterns of coexpression of the T1R genes in TRC: The first pattern is coexpression of T1R1 and T1R3 (in fungiform and palate taste buds), the second pattern is coexpression of T1R2 and T1R3 (in circumvallate, foliate and palate taste buds), and the third pattern is expression of only T1R3 (in fungiform and palate taste buds) (120, 123, 127).

Coexpression of T1R3 with either T1R1 or T1R2 in the same TRC suggested that they may function as heterodimers, which is believed to commonly occur with GPCRs (134). This pattern of coexpression also suggested that taste responses to sweeteners mediated by the T1R2 + T1R3 receptor combination should predominantly occur in the glossopharyngeal nerve that innervates the circumvallate taste buds, and that umami/L–amino acid taste responses mediated by the T1R1 + T1R3 receptor combination should

predominantly occur in the chorda tympani nerve that innervates fungiform taste buds. However, this does not correspond to results of electrophysiological studies that show that both chorda tympani and glossopharyngeal nerves respond to sweet and umami taste stimuli (47, 74, 131, 132).

A subsequent study in mice has shown that TRCs in both fungiform and circumvallate papillae express each T1R receptor alone and in all possible combinations (T1R1 + T1R2, T1R1 + T1R3, T1R2 + T1R3, and T1R1 + T1R2 + T1R3) (86). Similarly, it was found that human fungiform taste buds express all three T1R genes, with some fungiform TRC coexpressing T1R2 and T1R3 (101). These results are in a better agreement with electrophysiological responsiveness of the chorda tympani and glossopharyngeal nerves. They also suggest the existence of T1R1 + T1R2 heterodimers and homodimers for each T1R receptor. Coexpression of the T1R1 and T2R genes in mice has also been reported (86).

Ligands

T1R receptor-ligand interactions were characterized in two types of studies. In vitro heterologous expression experiments analyzed responses to taste stimuli in cells transfected with T1Rs. In vivo experiments examined effects of *Tas1r* genotypes on taste responses in mice. Two types of gene variation were studied in vivo: targeted mutations disrupting a gene (46, 179) and natural allelic variation (78) (these results are summarized in **Supplemental Table 3**).

Heterologously expressed T1R2 + T1R3 responds to a large number of sweeteners. The in vitro system reproduces in vivo species differences in sweet taste sensitivity. Several sweeteners (aspartame, cyclamate, neohesperidin dihydrochalcone, neotame, and sweet proteins) are perceived as sweet by humans but not rodents (e.g., 17, 48, 77). Correspondingly, human—but not rodent—T1R2 + T1R3 responds to these sweeteners. Heterologously expressed T1R1 + T1R3 functions as a broadly tuned L-amino acid receptor in mice and as a more narrowly tuned umami receptor in humans.

Experiments involving heterologous expression of combinations of T1Rs from different species (including interspecies receptor chimeras and receptors with mutations created at the interspecies variant sites) characterized the functional importance of different domains of T1R proteins. These studies have shown that human T1R1 determines higher T1R1 + T1R3 receptor selectivity for glutamate relative to the mouse receptor (126). Human T1R2 confers responsiveness of the T1R2 + T1R3 receptor to aspartame, glycyrrhizic acid, neotame, thaumatin, brazzein, and monellin (83, 126, 169, 179). The extracellular N-terminal domain of T1R2 is involved in recognition of aspartame (80, 176), neotame (176), D-tryptophan, and sucrose (80). The transmembrane domain of T1R2 is required for G-protein coupling of the T1R2 + T1R3 receptor (176). Responsiveness of the T1R2 + T1R3 receptor to cyclamate and neohesperidin dihydrochalcone, and its sensitivity to a sweet taste inhibitor lactisole, depend on the presence of human T1R3 (83, 178), specifically its transmembrane domain (81, 82, 169, 176). The cysteine-rich region of T1R3 is involved in recognition of brazzein and monellin (83).

For some ligands, interaction with both T1R2 and T1R3 receptor subunits has been demonstrated. Responsiveness to brazzein and monellin depends on interaction with both human T1R2 and human T1R3 (83). Binding assays have shown that N-terminal domains of mouse T1R2 and T1R3 bind sweeteners (glucose, sucrose, and sucralose), though with distinct affinities and conformational changes: Relative to T1R2, T1R3 binds sucrose with higher affinity and glucose with lower affinity (130).

Consistent with the in vitro results, *Tas1r1* knockout mice are deficient in taste responses to L-amino acids and umami stimuli, *Tas1r2* knockout mice are deficient in taste responses

to sweeteners, and *Tas1r3* knockout mice are deficient in taste responses to all these stimuli (46, 179). Variation of naturally occurring *Tas1r3* alleles in inbred mouse strains (78) has a pattern of effects not completely identical to effects of *Tas1r3* disruption in knockout mice. *Tas1r3* allelic variation affects taste responses to sweeteners (including D-amino acids) but not to L-amino acids, nonchiral glycine, or umami taste stimuli. This pattern is more similar to changes found in *Tas1r2* knockout mice. The likely reason for this is that the null allele of *Tas1r3* prevents the formation of heteromeric receptors with both T1R1 and T1R2, thus affecting responses to all ligands of these receptors. Natural allelic variation of *Tas1r3* affects binding affinity of the T1R3 protein for sweeteners (130), but it does not affect responses of heterologously expressed T1R1 + T1R3 to amino acids (126), which corresponds to effects of *Tas1r3* polymorphisms in vivo. The lack of effect of the natural allelic variation of *Tas1r3* on taste responses to ligands of the T1R1 + T1R3 receptor can be explained by several possible mechanisms: (*a*) ligand binding to the T1R3 receptor at a site that is not affected by the polymorphic variants, (*b*) ligand binding to the T1R1 receptor, or (*c*) the existence of another taste receptor binding these ligands.

In *Tas1r2* and *Tas1r3* knockout mice, concentrated solutions of sugars elicited reduced, but not completely eliminated, taste responses (46, 179). These residual responses were completely eliminated in *Tas1r2/Tas1r3* double-knockout mice (179). This suggests that T1R2 and T1R3 may function on their own as low-affinity sugar receptors, probably as homodimers. Consistent with this hypothesis, heterologously expressed T1R3 alone responded to 0.5 *M* sucrose, but not to lower sucrose concentrations (<0.3 M) or to artificial sweeteners (179). Heterologously expressed T1R3 alone was also reported to respond to a sugar trehalose (8); however, another study reported that trehalose induced significant receptor-independent rises in Ca^{2+}, and thus its use in a heterologous system was impractical (179). No responses to sweeteners were reported in cells with heterologously expressed T1R2 alone.

The data on ligand specificity of the T1R receptors suggest that perception of most of sweet and umami taste stimuli occurs via activation of these receptors. This is consistent with results of some human perception studies (31, 32). However, the existence of additional sweet or umami taste receptors is not precluded, and several candidates are described in a following section.

Allelic Variation of T1R Genes and Its Role in Individual Variation in Taste Responses

Within-species variation of the T1R genes has been examined in individual humans of different ethnicities and in strains of rats and mice. In rats and mice, the association of variants of the *Tas1r3* gene with sweetener taste responses has been analyzed.

Humans. Humans differ in perception of sweet taste, but genetic determination of this variation has not been unequivocally established (138, 140). In humans of African, Asian, European, and Native American origin, all three *TAS1R* genes have multiple polymorphisms, which include those resulting in amino acid changes of T1R proteins and even in a premature stop codon in *TAS1R1*. The majority of amino acid sequence variation occurs in the N-terminus extracellular domain, where taste ligands are likely to bind the taste receptors. *TAS1R2* was particularly diverse compared with other human genes: Its rate of polymorphisms was higher than average, in the top 5% to 10% of all human genes surveyed. Thus, *TAS1R* variation in human populations was predicted to contribute more to variation in sweet taste (which depends on *TAS1R2* and *TAS1R3*) than to variation in umami taste (which depends on *TAS1R1* and *TAS1R3*) (89).

Rats. Several rat strains with different saccharin preferences did not differ in protein sequence of T1R3. Some nonprotein-coding *Tas1r3* variants found among these strains were not associated with marked differences in *Tas1r3* expression and thus are unlikely to affect T1R3 function. Therefore, the prominent rat strain differences in saccharin preferences depend on genes other than *Tas1r3* (107).

Mice. In initial studies that identified the mouse *Tas1r3* gene, several polymorphisms associated with sweetener preferences were detected (91, 120, 123, 127, 147). However, these studies lacked proper quantitative analyses of gene-phenotype associations. Reed et al. (137) conducted a comprehensive quantitative analysis of the *Tas1r3* sequence variants associated with saccharin preference using 30 genealogically diverse inbred mouse strains. Of the 89 polymorphisms detected within the ~6.7 kb genomic region including the *Tas1r3* gene, eight were significantly associated with saccharin preferences. An absence of differences in the *Tas1r3* gene expression in the taste tissues of mice with different *Tas1r3* alleles suggested that the receptor function is likely to be affected by polymorphisms that change amino acid sequence of the T1R3 protein. A coding polymorphism with the strongest association with saccharin preferences resulted in the amino acid substitution of isoleucine to threonine at position 60 (I60T) in the extracellular N-terminus of the predicted T1R3 protein. Modeling of the T1R3 protein using the structure of the related mGluR1 receptor as a prototype has suggested that the I60T substitution introduces an extra N-terminal glycosylation site, which could affect dimerization of the receptor (120). However, this was not confirmed in a coimmunoprecipitation experiment (126). It was also suggested that this type of polymorphism could affect ligand binding (137). This prediction was subsequently confirmed in an in vitro study showing that a corresponding site-directed mutation changes binding affinity of the T1R3 protein to several sweeteners (130).

PROP: 6-n-propyl-2-thiouracil

Other Candidate Receptors for Sweet and Umami Tastes

Several molecules have been proposed as candidate mammalian taste receptors for umami or glutamate taste, including splice variants of metabotropic glutamate receptors, mGluR4 and mGluR1, and the N-methyl-D-aspartate-type glutamate ion channel receptor (30, 39a, 148, 160). Some sweet-tasting compounds can penetrate TRC membrane and act on intracellular targets (125). Thus, these biological molecules may function as intracellular receptors of such compounds.

T2R RECEPTORS

Discovery

The existence of a family of bitter taste receptors was predicted more than ten years ago by I. Lush, a geneticist who studied mouse strain differences in bitter taste avoidance, and who suggested that a cluster of bitterness-tasting genes "have evolved from one original bitterness gene by a process of local duplication and differentiation" (115). The T2R genes were discovered in 2000 by two groups. These discoveries were based on analyses of the recently released human genome sequences in the genome regions linked to bitter taste responsiveness in humans and mice. Adler et al. (6) examined a region of human chromosome 5 linked to perception of a bitter compound 6-n-propyl-2-thiouracil (PROP) (139) and discovered a novel GPCR, *TAS2R1*. Similarity searches of genomic DNA revealed additional related genes in human chromosomes 7 and 12. Although the *TAS2R1* gene is a candidate for the PROP sensitivity locus, which suggests that this is a bitter taste receptor for PROP, this relationship has not been experimentally proven yet, and T2R1 ligands are still not known. Matsunami et al. (118) examined a region of human chromosome 12 with

PLCβ2: phospholipase Cβ2

conserved synteny to a region of mouse chromosome 6 containing the sucrose octaacetate aversion (*Soa*) locus (13, 36, 115) and discovered *TAS2R* genes based on their weak similarity to a vomeronasal receptor gene. Several subsequent publications have identified additional human, rat, and mouse *TAS2R* genes (42, 43, 174).

Genomic Organization

Current genomic databases (2, 4) list 43 human *TAS2R* genes (38 intact genes and 5 pseudogenes; **Supplemental Table 1**) on chromosomes 5, 7, and 12 (**Supplemental Figure 1**) and 40 mouse *Tas2r* genes (35 intact genes and 5 pseudogenes; **Supplemental Table 2**) on chromosomes 2, 6, and 15. The T2R genes are intronless (**Supplemental Figure 2**) and encode ~300–330 amino acid GPCR proteins with a short N-terminal extracellular domain (**Figure 1**).

Tissue Expression

The main sites of expression of the T2R genes in mammals are TRCs of the circumvallate, foliate, palate, and epiglottis taste buds, and to a lesser degree fungiform taste buds (6, 9, 21, 33, 34, 93, 118). In mammals, T2R and T1R genes are expressed in different subsets of TRC (127) (but see 86).

It appears that multiple T2Rs are coexpressed in the same TRC, and possibly nearly all T2Rs are expressed in each T2R-positive TRC (6). The largely overlapping expression of the T2R genes within individual TRCs has been confirmed in a transgenic "rescue" experiment. In bitter taste–deficient phospholipase Cβ2 (PLCβ2) knockout mice, PLCβ2 was reintroduced under the control of three different *Tas2r* gene promoters. Responsiveness to all bitter taste stimuli examined (presumably acting on different T2R receptors) was restored in each of the transgenic lines produced with different constructs (124). However, results of another study (118) suggested that different TRCs may express different T2Rs.

The pattern of T2R expression has implications for bitter taste coding. Coexpression of multiple T2Rs in the same TRCs (6, 124) is consistent with behavioral discrimination and generalization data in primates and rats suggesting an identical taste quality perception of different bitter compounds (10, 154) and with neurophysiological data showing that responses to different bitter taste stimuli activate similar groups of neurons in the rat nucleus of the solitary tract (37) and in the primate cortex (152). On the other hand, expression of different T2Rs in different TRCs (118) is consistent with neurophysiological data showing that different bitter taste stimuli activate different TRCs (35) and afferent peripheral gustatory neurons (45) in rats and with the lack of conditioned taste aversion generalization between some bitter taste stimuli in hamsters (56). These latter data suggest that the taste system can discriminate among different bitter taste stimuli. It was proposed that a discrepancy between expression of multiple T2Rs in the same TRC and selective responses of TRCs to bitter tastants might be due to differences in levels of expression of the same T2R in different TRCs. This would result in variation among individual T2R-expressing cells in their sensitivity to bitter tastants, although each of these TRCs still would respond to multiple bitter ligands (38).

Ligands

The number of compounds perceived by humans as bitter (65) is much larger than the number of human *TAS2R* genes, implying that each human T2R responds to more than one bitter ligand (22). The same is likely to be true for other species. Some T2Rs interact with a wide range of bitter-tasting ligands (e.g., *TAS2R14* and *TAS2R16*; see **Supplemental Table 4**), which supports this expectation. However, some other T2Rs appear to have narrow ligand specificities. It has been suggested that different T2R alleles may

have different profiles of ligand specificity (87, 122). Thus, the repertoire of bitter taste receptors may be not limited by a number of the T2R genes, but may involve as many receptors as there are T2R alleles (122).

Ligands have been determined for only a relatively small number of T2Rs in four vertebrate species: humans, chimpanzees, rats, and mice (**Supplemental Table 4**). All of the compounds that interact with T2Rs evoke bitter taste sensation in humans. The T2R ligand specificities have been determined predominantly using in vitro studies. For the following six T2Rs, ligand specificity was examined both in vitro and in vivo with matching results, which provides compelling evidence that these T2Rs function as bitter taste receptors.

Mouse *Tas2r105* gene is located in the genomic region of the *Cyx* (cycloheximide tasting) locus (11, 114) on distal chromosome 6. *Tas2r105* coding sequence variants are associated with behavioral sensitivity to cycloheximide in several inbred mouse strains (39, 128). Cells heterologously expressing *Tas2r105* respond to cycloheximide. Expression of a *Tas2r105* allele from a cycloheximide taster strain results in higher cell responsiveness than does expression of an allele from a nontaster strain (39). *Tas2r105* knockout mice show selective impairment in neural and behavioral responses to cycloheximide but not to other bitter or nonbitter taste stimuli (124).

Although these data provide strong evidence that the *Tas2r105* gene is identical to the *Cyx* locus and encodes a receptor binding cycloheximide, some other data do not agree with this hypothesis. Chandrashekar et al. (39) examined strain distribution patterns of *Tas2r105* genotypes and *Cyx* phenotypes in BXD recombinant inbred strains and found a tight linkage but not perfect concordance between these loci; they have explained this discordance by ambiguity in designation of the *Cyx* phenotype of the BXD strains by Lush & Holland (114). However, the study of Lush & Holland (114) has shown a clearly dichotomous strain distribution pattern of the BXD strains. But, strangely, the progenitors of the BXD strains had similar responsiveness to cycloheximide: The average preference scores for 1 μM cycloheximide were 22% in the C57BL/6 inbred strain and 29% for the DBA/2 strain. Both progenitor strains were similar to a group of BXD strains that formed a cluster of sensitive strains with an average preference score for 1 μM cycloheximide of 18%, as opposed to a group of relatively insensitive BXD strains with an average preference score 41% (114). Consistent with these data, no differences were found between C57BL/6 and DBA/2 strains in brief-access responses to cycloheximide in a recent study (29). In addition, preference scores for cycloheximide were continuously distributed among 27 inbred strains (114), which does not allow them to be categorized as tasters and nontasters. Thus, analysis of *Tas2r105* sequence variants between strains assumed to be tasters (CBA/Ca, BALB/c, C3H/He, and DBA/2) and nontasters (C57BL/6 and 129/Sv) (39) is questionable. An additional limitation of this analysis is that the four taster strains have shared genealogy (20) and thus are likely to share many parts of the genome due to identity-by-descent, and not necessarily because of a true genotype-phenotype association. These inconsistencies require additional studies to resolve. A quantitative analysis of genotype-phenotype associations in genealogically diverse strains (e.g., 137) would provide more conclusive data.

Orthologous human *TAS2R4* and mouse *Tas2r108* respond to denatonium and PROP in a heterologous system (39). Transgenic expression of each gene in the chemosensory neurons of *Caenorhabditis elegans* affected behavioral responses of worms to denatonium and PROP (44).

Human *TAS2R16* responds to β-glucopyranosides in the heterologous expression system (34). Naturally occurring human *TAS2R16* alleles have different responsiveness to several β-glucopyranosides in vitro (69, 153). It is unknown whether these alleles are also associated with human perception

PTC: phenylthiocarbamide

of β-glucopyranoside bitterness. Although wild-type mice are indifferent to phenyl-β-D-glucopyranoside, mice with a human *TAS2R16* transgene expressed in bitter-sensing cells under control of the mouse *Tas2r119* promoter avoid phenyl-β-D-glucopyranoside in behavioral tests. Mice with human *TAS2R16* transgene expressed in sweet-sensing cells under control of the mouse *Tas1r2* promoter show preference for phenyl-β-D-glucopyranoside (124). Transgenic expression of human *TAS2R16* in the chemosensory neurons of *C. elegans* affected behavioral responses of worms to phenyl-β-D-glucopyranoside (44).

Human *TAS2R38* was demonstrated in a positional cloning study (88) as a gene identical to a human phenylthiocarbamide (PTC) bitter taste sensitivity locus on chromosome 7q (50). *TAS2R38* has three common missense single nucleotide polymorphisms resulting in substitutions of proline to alanine at amino acid position 49 (P49A), alanine to valine at position 262 (A262V), and valine to isoleucine at position 296 (V296I). These polymorphisms give rise to several haplotypes, the most common of which are PAV (PTC-sensitive allele) and AVI (PTC-insensitive allele) (88, 173). *TAS2R38* genotypes are associated with human perception of PTC and PROP bitterness (33, 52, 121, 135). Cells heterologously expressing the sensitive PAV alleles of *TAS2R38* respond to thioamides (including PTC and PROP). PTC and PROP responses of cells heterologously expressing different alleles of *TAS2R38* correlate with psychophysical responses of individuals carrying these alleles (33). Although wild-type mice do not show strong lick suppression in response to PTC solutions in brief-access tests (128), mice with a taster (PAV) allele of human *TAS2R38* transgenically expressed in bitter-sensing cells under the control of a mouse *Tas2r* promoter show strong aversion to PTC (124).

Although a PTC nontaster allele of human *TAS2R38* (AVI) is expressed in taste buds, it does not respond to taste stimuli in vitro (33). Because taster and nontaster alleles of *TAS2R38* are maintained by balanced selection (173), it was suggested that the nontaster allele may serve as a receptor for as yet unidentified toxic bitter substances other than PTC (87, 173).

Allelic variants of chimpanzee *TAS2R38*, an ortholog of human *TAS2R38*, are also associated with taste sensitivity to PTC in individual animals. A taster allele of chimpanzee *TAS2R38* responds to PTC in vitro (172).

Allelic Variation of T2R Genes and Its Role in Individual Variation in Taste Responses

Humans. Individual humans differ in bitter taste perception, and some of this variation has a genetic component (140). Human *TAS2R* genes have substantial diversity of coding sequence (87, 122, 161, 167), which suggests that *TAS2R* polymorphisms may be responsible for the genetic component of individual differences in bitter taste.

However, this relationship has been demonstrated only for one gene, *TAS2R38*. It is located on chromosome 7, where linkages for PTC and PROP taste sensitivity have been detected (40, 41, 50, 135, 139). Allelic variants of *TAS2R38* explain more than 50% of phenotypical variation in PTC sensitivity (88) and are also associated with human perception of PROP bitterness (33, 52, 121, 135).

Significant or suggestive linkages have been also detected on chromosomes 1, 3, 10, and 16 for PTC taste sensitivity (50) and on chromosome 5 for PROP taste sensitivity (139). The PROP sensitivity locus on human chromosome 5 (139) includes the *TAS2R1* gene but no other *TAS2R* genes. However, the identity of the PROP sensitivity locus and the *TAS2R1* gene has not yet been proven. The PTC sensitivity loci in chromosomes 1, 3, 10, and 16 (50) contain no *TAS2R* genes. Identification of genes corresponding to the genetic loci for bitter taste sensitivity, and matching variation in *TAS2R* sequences with

individual variation in bitter taste perception, are important areas for future studies.

Hamsters, rats, and mice. Strain differences in behavioral responses to bitter taste stimuli were found in rats (159) and hamsters (57), but most research on genetics of taste has been conducted in mice. Mouse strains differ in behavioral and neural responses to bitter taste stimuli (e.g., 27, 29, 76, 108–112, 114). Several linked genetic loci on mouse chromosome 6, in a *Tas2r* gene–cluster region, are responsible for variation in aversion to bitter-tasting quinine (*Qui*), cycloheximide (*Cyx*), copper glycinate (*Glb*), and acetylated sugars, sucrose octaacetate and raffinose undecaacetate (*Soa/Rua*) (11, 13, 26, 36, 66, 67, 76, 108, 110, 112, 114, 115, 129, 168).

A few studies conducted so far have detected considerable variation in sequences of the mouse *Tas2r* genes (39, 128, 129). All this strongly suggests that the genetic variation in taste responses to the bitter compounds is due to polymorphisms of the *Tas2r* genes, as was predicted by Lush et al. (115). However, this relationship has been demonstrated only for the *Tas2r105* gene corresponding to the *Cyx* locus (39, 124, 128), although with some inconsistencies (see Ligands section, above). There is also evidence for additional linkages of mouse bitter taste responses outside the *Tas2r* regions (68, 95, 129).

Other Candidate Receptors for Bitter Taste

In addition to activation of T2R receptor proteins, some bitter compounds can interact with ion channels in the cell membrane or with intracellular targets (125, 145, 150). Thus, these proteins may also function as receptors for these compounds.

OTHER TASTE RECEPTORS

Candidate Sour Taste Receptors

A commonly accepted view is that the taste receptors for sour (H^+) and salty (Na^+) tastes are ion channels (25, 49). Several candidate sour (acid) taste receptors have been proposed in recent years. One of these genes is a neuronal (degenerin) amiloride-sensitive cation channel 1 (see ACCN1 sidebar). It has been proposed as a sour taste receptor in rat (102, 105, 162–164). However, this channel is not expressed in mouse taste buds (143), and behavioral (90) and physiological (143) responses to sour taste stimuli are unaltered in mice lacking the *Accn1* gene. HCN1 and HCN4, members of a family of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (see HCN sidebar), were also proposed as putative sour receptors (156). However, Ca^{2+} responses of taste cells to acids were not inhibited by Cs^+, an inhibitor of HCN channels (141). Acid taste transduction involves intracellular acidification of TRC (116, 141), which is expected to affect acid-sensitive ion channel(s). Several two-pore domain potassium leak conductance channels from the K_2P family are sensitive to intracellular acidification and thus were examined as candidate acid taste transducers. Based on the gene expression pattern and pharmacological analysis, TASK-1 appears to be the most likely candidate (see TASK-1 sidebar), although other K_2P channels cannot be excluded (142). The Na^+-H^+-exchanger isoform 1 (NHE-1) (see NHE-1 sidebar) was also suggested to be involved in sour taste transduction based on its gene expression and pharmacological analyses (165).

Finally, the most recent studies suggest that the *Pkd1l3* and *Pkd2l1* genes (see PKD1L3 and PKD2L1 sidebar) participate in reception of sourness (73, 79, 106). However, their role in behavioral taste responses to sourness has not yet been demonstrated. In addition, some questions arising from the most recent studies have not been resolved. For example, acids activate the *Pdk2l1* protein in vitro only when it is coexpressed with *Pkd1l3* (79). Yet, disruption of *Pdk2l1*-expressing cells in the fungiform papillae abolishes CT responses to acids (73) despite lack of *Pkd1l3* expression in these cells (73,

ACCN1

In humans, the neuronal (degenerin) amiloride-sensitive cation channel 1 is encoded by the *ACCN1* gene on chromosome 17q11 [gene name: amiloride-sensitive cation channel 1, neuronal (degenerin); other symbols: *ACCN*, *ASIC2a*, *ASIC2*, *BNC1*, *BNaC1*, *hBNaC1* and *MDEG*]. In the mouse, it is encoded by the *Accn1* gene on chromosome 11 [gene name: amiloride-sensitive cation channel 1, neuronal (degenerin); other symbols: *ASIC2*, *BNaC1a*, *BNC1*, *Mdeg*]. *Accn1* is a member of a family of voltage-insensitive cation channels involved in mechanosensitivity and acid sensitivity. Its mRNA exists as two splice variants, described as ASIC2a and ASIC2b (166).

HCN

The human *HCN1* gene is on chromosome 5p12 (gene name: hyperpolarization activated cyclic nucleotide-gated potassium channel 1; other names: *BCNG1*, *BCNG-1*, *HAC-2*). The mouse *Hcn1* gene is on chromosome 13 (gene name: hyperpolarization-activated, cyclic nucleotide-gated K^+ 1; other names: *Bcng1*, *HAC2*). The human *HCN4* gene is on chromosome 15q24 (gene name: hyperpolarization activated cyclic nucleotide-gated potassium channel 4). The mouse *Hcn4* gene is on chromosome 9 (gene name: hyperpolarization-activated, cyclic nucleotide-gated K^+ 4).

TASK-1

In humans, the TASK-1 channel protein is encoded by the *KCNK3* gene on chromosome 2p23 (gene name: potassium channel, subfamily K, member 3; other names: *TASK*, *TASK-1*). Its mouse ortholog is *Kcnk3* on chromosome 5 (gene name: potassium channel, subfamily K, member 3; other names: *cTBAK-1*).

79). This suggests the existence of another, yet unknown partner for heteromerization with *Pdk2l1*.

Candidate Salty Taste Receptors

A large number of studies suggested that at least in rodents, Na^+ taste reception involves the selective epithelial amiloride-sensitive sodium channel, ENaC, which is a member of the degenerin/ENaC superfamily of ion channels (for reviews, see 28, 103). In humans, there are four ENaC channel subunits, α, β, γ, and δ. Mice and rats lack the ENaC δ subunit (85) (see ENaC sidebar). A variant of a vanilloid (capsaicin) receptor-1 has been proposed as an amiloride-insensitive salt taste receptor in rodents (117) (see TRPV1 sidebar). However, the evidence for ENaC or other candidate salt taste receptors in vertebrate is not as convincing as it is for the T1R and T2R receptors. The strongest evidence for involvement of degenerin/ENaC channel genes in Na^+ taste responses was found for the *ppk11* and *ppk19* genes in *Drosophila* (104).

Taste Detection of Lipids

The predominant orosensory cue for fat itself is its texture (119). Fat may also be detected by the presence of its decomposition products or impurities (136), which can activate olfactory or gustatory systems. Recent data suggest that taste may play a more important role in detection of dietary lipids than was previously believed. Dietary lipids consist mainly of triglycerides, but the lingual lipase hydrolyzes triglycerides and releases free fatty acids in the oral cavity where they can access TRCs and affect their function. Free fatty acids were shown to inhibit the delayed rectifying potassium channels in rat TRCs (63). In addition, the fatty acid transporter CD36 is expressed in TRCs and may be involved in oral detection of fatty acids (59, 94, 177) (see CD36 sidebar).

Taste Detection of Complex Carbohydrates

Rats and some other species may also perceive a taste of polysaccharides and starch, which is qualitatively distinct from the taste of sugars (151). A molecular mechanism of gustatory reception of these complex carbohydrates is

unknown, but there is evidence that it does not involve the T1R3 receptor (75).

Taste Detection of Water

Water consumption is crucial for animals' survival and is regulated by thirst, a specialized water appetite. This suggests that animals have mechanisms for chemosensory detection of water or hypo-osmotic fluids. Consistent with this, water can evoke taste responses (62). It was suggested that TRCs act as osmotic sensors and that transduction of hypo-osmotic stimuli involves water influx through aquaporins followed by activation of volume-regulated anion channels (62). Several aquaporin molecules are expressed in TRC, with the apically expressed AQP5 being the most likely candidate for water taste transduction (62, 64) (see AQP5 sidebar).

Taste perception of water by humans largely depends on the adaptation state of the oral cavity. Adaptation to different taste solutions (and probably to saliva) affects how water is perceived (18). Water elicits a strong sweet taste when it is applied to the oral cavity after exposure to sweet taste blockers. This phenomenon has been labeled "sweet water aftertaste" (51). This adaptation-dependent perception of water taste could involve central mechanisms, intracellular adaptation within TRC, or interactions at the receptor level. A recent in vitro study with a heterologously expressed T1R2 + T1R3 receptor demonstrated that sweet water aftertaste is explained by interactions at the receptor level. This study suggested that the sweet taste receptor shifts from an inactive state (when it is exposed to a sweet taste inhibitor) to an active state (upon rinsing with water), which initiates transduction events and results in perception of sweetness (61).

TASTE RECEPTORS IN NONTASTE TISSUES AND INTERNAL CHEMOSENSATION

Some substances detected by the gustatory system as taste stimuli also need to be detected inside the body for homeostatic regulation. There are interoceptive mechanisms for detecting sodium, pH, glucose, and amino acids in different internal organs, such as the kidney, pancreas, gut, and brain. This raises the possibility that the same receptors can serve as

NHE-1

In humans, the NHE-1 protein is encoded by the *SLC9A1* gene on chromosome 1p36 [gene name: solute carrier family 9 (sodium/hydrogen exchanger), member 1 (antiporter, Na^+/H^+, amiloride sensitive); other symbols: *APNH*, *NHE1*]. Its mouse ortholog is *Slc9a1* on chromosome 4 [gene name: solute carrier family 9 (sodium/hydrogen exchanger), member 1; other symbols: antiporter, *Apnh*, Na^+/H^+, amiloride sensitive, *Nhe1*].

PKD1L3 AND PKD2L1

The human *PKD1L3* gene is on chromosome 16q22 (gene name: polycystic kidney disease 1-like 3); its mouse ortholog is *Pkd1l3* on chromosome 8 (gene name: polycystic kidney disease 1 like 3). The human *PKD2L1* gene is on chromosome 10q24 (gene name: polycystic kidney disease 2-like 1; other symbols: *PKD2L*, *PKDL*). Its mouse ortholog is *Pkd2l1* on chromosome 19 (gene name: polycystic kidney disease 2-like 1; other symbols: *PCL*, *PKD2L*, *Pkdl*, polycystin-L, *TRPP3*).

ENaC

The four human ENaC channel subunits, α, β, γ, and δ, are encoded respectively by four genes: *SCNN1A* (alias: *ENaCa*) on chromosome 12p13, closely linked *SCNN1B* (alias: *ENaCb*) and *SCNN1G* (alias: *ENaCg*) on chromosome 16p12, and *SCNN1D* (aliases: *dNaCh*, *ENaCd*) on chromosome 1p36 (gene names: sodium channel, nonvoltage-gated 1 alpha, beta, gamma, or delta; *SCNN1B* is also known as a gene responsible for Liddle syndrome). The three mouse ENaC channel subunits, α, β, and γ, are encoded respectively by three genes: *Scnn1a* on chromosome 6, and closely linked *Scnn1b* and *Scnn1g* on chromosome 7 (gene names: sodium channel, nonvoltage-gated, type I, alpha, beta, or gamma).

TRPV1

Human vanilloid receptor-1 is encoded by the *TRPV1* gene on chromosome 17p13 (gene name: transient receptor potential cation channel, subfamily V, member 1; previous name: vanilloid receptor subtype 1; previous symbol: *VR1*). Its mouse ortholog is *Trpv1* on chromosome 11 (gene name: transient receptor potential cation channel, subfamily V, member 1; other names: capsaicin receptor, *OTRPC1*, *VR-1*).

CD36

Human *CD36* gene is on chromosome 7q11 (gene name: CD36 molecule; previous names: CD36 antigen, collagen type I receptor, thrombospondin receptor; other symbols: *SCARB3*, *GPIV*, *FAT*, *GP4*, *GP3B*). Its mouse ortholog is *Cd36* on chromosome 5 (gene name: CD36 antigen; other symbols: *FAT*, fatty acid translocase, *Scarb3*).

AQP5

Human *AQP5* gene is on chromosome 12q13 (gene name: aquaporin 5); its mouse ortholog is *Aqp5* on chromosome 15 (gene name: aquaporin 5).

taste receptors and interoceptors. Although in some cases taste and interoception use different receptor mechanisms [e.g., for detection of glucose and sodium by brain (70, 96)], there are examples of sharing the same receptor protein by the two systems. The *Pkd2l1* channel is involved in pH sensing by the TRC and by neurons in the spinal cord (73). ENaC may also be a shared mechanism for sodium detection by TRC and other body tissues.

A number of studies have detected expression of the T1R and T2R genes in nontaste tissues. The T1R genes were found in testis (91, 92, 120), brain, thymus (120), gastrointestinal tract, enteroendocrine cells (24, 53, 120, 146), kidney, lymphocytes (92), liver, and pancreas (158). The T2R genes were found in testis (118), gastrointestinal tract, enteroendocrine cells (146, 174, 175), and nasal respiratory epithelium (55). This suggests that the taste receptors may be involved in the chemosensory function of these organs (155).

Ectopic expression of olfactory receptor genes similarly has raised questions about the role they play in nonolfactory tissues. A recent systematic analysis of olfactory receptor expression in different tissues suggested that only small olfactory receptor subsets might play functional roles in different tissues, while most of them are likely to be under a neutral transcription control (54). Similarly, caution should be exerted when offering a functional interpretation for ectopic expression of taste receptors until more comprehensive studies are conducted.

PRACTICAL APPLICATIONS OF TASTE RECEPTOR STUDIES

There is substantial interest in developing novel taste stimuli and taste modifiers for humans and other animals. For humans, areas of interest include making food and drinks healthier without sacrificing their palatability and making oral medications more acceptable to patients. A substantial demand exists for artificial sweet and umami compounds, enhancers of salty, sweet, and umami taste, blockers of bitter taste, and pharmaceutical compounds with improved sensory properties. There is also a demand for improvement in the taste quality of food for companion and farm animals and for developing nonlethal repellents of wild animals, e.g., nontoxic chemicals with aversive taste. Development of such products has been hampered by lack of knowledge of the molecular identity of the taste receptors. Discovery of taste receptors, characterization of their active sites involved in interactions with agonists and antagonists, and development of high-throughput techniques for in vitro screening of taste stimuli will facilitate the design of novel taste-active compounds.

Allelic variation of human taste receptors can affect food perception, choice, and

consumption. As a result, it can influence nutrition and potentially predispose individuals to certain diseases (e.g., 19). Thus, some taste receptor alleles can be disease risk factors. Genotypes of these receptors may be useful as biological markers to identify predispositions to some diseases and to suggest interventions for disease prevention. Available data provide some examples for the role of taste receptor variation in human nutrition and health.

Sensitive alleles of human *TAS2R38* receptor respond to PTC, PROP, and related compounds that contain a thiourea (N – C = S) moiety. Some plants consumed by humans contain glucosinolates, compounds that also contain the thiourea moiety. A recent study has shown that *TAS2R38* genotype affects perception of bitterness of glucosinolate-containing plants, such as broccoli, turnip, and horseradish (149). Allelic variation of *TAS2R38* may have even more widespread effects on food choice, as it was shown to be associated with preferences for sucrose and sweet-tasting beverages and foods in children (but not adults) (121).

Taste receptor variation may be a biomarker of predisposition to alcoholism. Ethanol flavor has bitter and sweet taste components. Variation in bitter and sweet taste responsiveness is associated with perception of ethanol flavor and consumption of alcoholic beverages (12). In mice, allelic variation of the *Tas1r3* sweet taste receptor gene is associated with voluntary ethanol consumption (15). Although hedonic responses to sweet taste are considered as one of the biomarkers of predisposition to alcoholism in humans (84), genes responsible for this association are still unknown. Higher sensitivity to ethanol bitterness may protect against excess alcohol consumption. Consistent with this hypothesis, individuals carrying one or two sensitive (PAV) alleles of the PTC receptor gene, *TAS2R38*, had lower yearly consumption of alcoholic beverages than did individuals homozygous for the insensitive allele, AVI (52). Similarly, there is an association between risk of alcohol dependence and *TAS2R16* (β-glucopyranosides receptor) polymorphisms: An ancestral K172 allele, which is less sensitive to β-glucopyranosides in vitro, is associated with increased risk of alcohol dependence (69).

CONCLUDING REMARKS

Taste receptors function as one of the interfaces between internal and external milieus. Tremendous progress has been achieved in the past few years with the discovery of the T1R and T2R receptors and the understanding of their function. Individual differences in taste, at least in some cases, can be attributed to allelic variants of the taste receptor genes. Understanding how taste receptors interact with taste stimuli and identifying their patterns of expression in taste cells shed light on coding of taste information by the nervous system.

However, many challenging tasks remain before we fully understand how taste works. Much of this important future research must be done with taste receptor genes. The important questions to be addressed include finding genes that encode a complete repertoire of taste receptors for different taste qualities, as well as genes that encode proteins involved in taste transduction and transmission, taste bud cell turnover, and connectivity between taste cells and afferent nerves. Studies of allelic variation of taste receptors will help to elucidate individual differences in taste perception, food choice, nutrition, and health, and to understand functional organization of receptor domains and their ligand specificities.

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LITERATURE CITED

1. GPCRDB. *Information system for G protein-coupled receptors (GPCRs).* Accessed March 27, 2007. Nijmegen, Netherlands: GPCRDB Inform. Syst. **http://www.gpcr.org/7tm/**
2. Human Genome Database. Accessed March 27, 2007. Baltimore, MD: GDB. **http://www.gdb.org**
3. The Human Genome Organisation (HUGO) Gene Nomenclature Committee. Accessed March 27, 2007. London: HUGO. **http://www.gene.ucl.ac.uk/nomenclature/**
4. Mouse Genome Informatics. Accessed March 27, 2007. Bar Harbor, ME: Jackson Lab. **http://www.informatics.jax.org**
5. Rules for Nomenclature of Genes, Genetic Markers, Alleles, and Mutations in Mouse and Rat. Accessed March 27, 2007. Bar Harbor, ME: Jackson Lab. **http://www.informatics.jax.org/mgihome/nomen/gene.shtml**
6. Adler E, Hoon MA, Mueller KL, Chandrashekar J, Ryba NJP, Zuker CS. 2000. A novel family of mammalian taste receptors. *Cell* 100:693–702
7. Andres-Barquin PJ, Conte C. 2004. Molecular basis of bitter taste: the T2R family of G protein-coupled receptors. *Cell Biochem. Biophys.* 41:99–112
8. Ariyasu T, Matsumoto S, Kyono F, Hanaya T, Arai S, et al. 2003. Taste receptor T1R3 is an essential molecule for the cellular recognition of the disaccharide trehalose. *In Vitro Cell Dev. Biol. Anim.* 39:80–88
9. Asano-Miyoshi M, Abe K, Emori Y. 2001. IP(3) receptor type 3 and PLCbeta2 are coexpressed with taste receptors T1R and T2R in rat taste bud cells. *Chem. Senses* 26:259–65
10. Aspen J, Gatch MB, Woods JH. 1999. Training and characterization of a quinine taste discrimination in rhesus monkeys. *Psychopharmacology (Berl.)* 141:251–57
11. Azen EA, Lush IE, Taylor BA. 1986. Close linkage of mouse genes for salivary proline-rich proteins (PRPs) and taste. *Trends Genet.* 2:199–200
12. Bachmanov AA, Kiefer SW, Molina JC, Tordoff MG, Duffy VB, et al. 2003. Chemosensory factors influencing alcohol perception, preferences, and consumption. *Alcohol. Clin. Exp. Res.* 27:220–31
13. Bachmanov AA, Li X, Li S, Neira M, Beauchamp GK, Azen EA. 2001. High-resolution genetic mapping of the sucrose octaacetate taste aversion (*Soa*) locus on mouse chromosome 6. *Mamm. Genome* 12:695–99
14. Bachmanov AA, Li X, Reed DR, Ohmen JD, Li S, et al. 2001. Positional cloning of the mouse saccharin preference (*Sac*) locus. *Chem. Senses* 26:925–33
15. Bachmanov AA, Reed DR, Li X, Li S, Beauchamp GK, Tordoff MG. 2002. Voluntary ethanol consumption by mice: genome-wide analysis of quantitative trait loci and their interactions in a C57BL/6ByJ × 129P3/J F2 intercross. *Genome Res.* 12:1257–68
16. Bachmanov AA, Reed DR, Ninomiya Y, Inoue M, Tordoff MG, et al. 1997. Sucrose consumption in mice: major influence of two genetic loci affecting peripheral sensory responses. *Mamm. Genome* 8:545–48
17. Bachmanov AA, Tordoff MG, Beauchamp GK. 2001. Sweetener preference of C57BL/6ByJ and 129P3/J mice. *Chem. Senses* 26:905–13
18. Bartoshuk LM. 1977. Water taste in mammals. In *Drinking Behavior: Oral Stimulation, Reinforcement, and Preference*, ed. JAWM Weijnen, J Mendelson, pp. 317–39. New York: Plenum

19. Basson MD, Bartoshuk LM, Dichello SZ, Panzini L, Weiffenbach JM, Duffy VB. 2005. Association between 6-n-propylthiouracil (PROP) bitterness and colonic neoplasms. *Dig. Dis. Sci.* 50:483–89
20. Beck JA, Lloyd S, Hafezparast M, Lennon-Pierce M, Eppig JT, et al. 2000. Genealogies of mouse inbred strains. *Nat. Genet.* 24:23–25
21. Behrens M, Brockhoff A, Kuhn C, Bufe B, Winnig M, Meyerhof W. 2004. The human taste receptor hTAS2R14 responds to a variety of different bitter compounds. *Biochem. Biophys. Res. Commun.* 319:479–85
22. Behrens M, Meyerhof W. 2006. Bitter taste receptors and human bitter taste perception. *Cell Mol. Life Sci.* 63:1501–9
23. Belknap JK, Crabbe JC, Plomin R, McClearn GE, Sampson KE, et al. 1992. Single-locus control of saccharin intake in BXD/Ty recombinant inbred (RI) mice: some methodological implications for RI strain analysis. *Behav. Genet.* 22:81–100
24. Bezencon C, le Coutre J, Damak S. 2007. Taste-signaling proteins are coexpressed in solitary intestinal epithelial cells. *Chem. Senses.* 32:41–49
25. Bigiani A, Ghiaroni V, Fieni F. 2003. Channels as taste receptors in vertebrates. *Prog. Biophys. Mol. Biol.* 83:193–225
26. Blizard DA, Kotlus B, Frank ME. 1999. Quantitative trait loci associated with short-term intake of sucrose, saccharin and quinine solutions in laboratory mice. *Chem. Senses* 24:373–85
27. Boughter JD, Bachmanov AA. 2007. Behavioral genetics and taste. *BMC Neurosci.* In press
28. Boughter JD Jr, Gilbertson TA. 1999. From channels to behavior: an integrative model of NaCl taste. *Neuron* 22:213–15
29. Boughter JD Jr, Raghow S, Nelson TM, Munger SD. 2005. Inbred mouse strains C57BL/6J and DBA/2J vary in sensitivity to a subset of bitter stimuli. *BMC Genet.* 6:36
30. Brand JG. 2000. Receptor and transduction processes for umami taste. *J. Nutr.* 130:942–45S
31. Breslin PA, Beauchamp GK, Pugh EN Jr. 1996. Monogeusia for fructose, glucose, sucrose, and maltose. *Percept. Psychophys.* 58:327–41
32. Breslin PA, Kemp S, Beauchamp GK. 1994. Single sweetness signal. *Nature* 369:447–48
33. Bufe B, Breslin PA, Kuhn C, Reed DR, Tharp CD, et al. 2005. The molecular basis of individual differences in phenylthiocarbamide and propylthiouracil bitterness perception. *Curr. Biol.* 15:322–27
34. Bufe B, Hofmann T, Krautwurst D, Raguse JD, Meyerhof W. 2002. The human TAS2R16 receptor mediates bitter taste in response to beta-glucopyranosides. *Nat. Genet.* 32:397–401
35. Caicedo A, Roper SD. 2001. Taste receptor cells that discriminate between bitter stimuli. *Science* 291:1557–60
36. Capeless CG, Whitney G, Azen EA. 1992. Chromosome mapping of *Soa*, a gene influencing gustatory sensitivity to sucrose octaacetate in mice. *Behav. Genet.* 22:655–63
37. Chan CY, Yoo JE, Travers SP. 2004. Diverse bitter stimuli elicit highly similar patterns of Fos-like immunoreactivity in the nucleus of the solitary tract. *Chem. Senses* 29:573–81
38. Chandrashekar J, Hoon MA, Ryba NJ, Zuker CS. 2006. The receptors and cells for mammalian taste. *Nature* 444:288–94
39. Chandrashekar J, Mueller KL, Hoon MA, Adler E, Feng L, et al. 2000. T2Rs function as bitter taste receptors. *Cell* 100:703–11
39a. Chaudhari N, Landin AM, Roper SO. 2000. Ametabotropic glutamate receptor variant functions as a taste receptor. *Nat. Neurosci.* 3:113–19

40. Chautard-Freire-Maia EA. 1974. Linkage relationships between 22 autosomal markers. *Ann. Hum. Genet.* 38:191–98
41. Conneally PM, Dumont-Driscoll M, Huntzinger RS, Nance WE, Jackson CE. 1976. Linkage relations of the loci for Kell and phenylthiocarbamide taste sensitivity. *Hum. Hered.* 26:267–71
42. Conte C, Ebeling M, Marcuz A, Andres-Barquin PJ. 2003. Identification of the T2R repertoire of taste receptor genes in the rat genome sequence. *Genome Lett.* 2:155–61
43. Conte C, Ebeling M, Marcuz A, Nef P, Andres-Barquin PJ. 2002. Identification and characterization of human taste receptor genes belonging to the TAS2R family. *Cytogenet. Genome Res.* 98:45–53
44. Conte C, Guarin E, Marcuz A, Andres-Barquin PJ. 2006. Functional expression of mammalian bitter taste receptors in *Caenorhabditis elegans*. *Biochimie* 88:801–6
45. Dahl M, Erickson RP, Simon SA. 1997. Neural responses to bitter compounds in rats. *Brain Res.* 756:22–34
46. Damak S, Rong M, Yasumatsu K, Kokrashvili Z, Varadarajan V, et al. 2003. Detection of sweet and umami taste in the absence of taste receptor T1r3. *Science* 301:850–53
47. Danilova V, Hellekant G. 2003. Comparison of the responses of the chorda tympani and glossopharyngeal nerves to taste stimuli in C57BL/6J mice. *BMC Neurosci.* 4:5
48. Danilova V, Hellekant G, Tinti JM, Nofre C. 1998. Gustatory responses of the hamster *Mesocricetus auratus* to various compounds considered sweet by humans. *J. Neurophysiol.* 80:2102–12
49. Desimone JA, Lyall V. 2006. Taste receptors in the gastrointestinal tract III. Salty and sour taste: sensing of sodium and protons by the tongue. *Am. J. Physiol. Gastrointest. Liver Physiol.* 291:G1005–10
50. Drayna D, Coon H, Kim UK, Elsner T, Cromer K, et al. 2003. Genetic analysis of a complex trait in the Utah Genetic Reference Project: a major locus for PTC taste ability on chromosome 7q and a secondary locus on chromosome 16p. *Hum. Genet.* 112:567–72
51. DuBois GE. 2004. Unraveling the biochemistry of sweet and umami tastes. *Proc. Natl. Acad. Sci. USA* 101:13972–73
52. Duffy VB, Davidson AC, Kidd JR, Kidd KK, Speed WC, et al. 2004. Bitter receptor gene (TAS2R38), 6-n-propylthiouracil (PROP) bitterness and alcohol intake. *Alcohol. Clin. Exp. Res.* 28:1629–37
53. Dyer J, Salmon KS, Zibrik L, Shirazi-Beechey SP. 2005. Expression of sweet taste receptors of the T1R family in the intestinal tract and enteroendocrine cells. *Biochem. Soc. Trans.* 33:302–5
54. Feldmesser E, Olender T, Khen M, Yanai I, Ophir R, Lancet D. 2006. Widespread ectopic expression of olfactory receptor genes. *BMC Genomics* 7:121
55. Finger TE, Bottger B, Hansen A, Anderson KT, Alimohammadi H, Silver WL. 2003. Solitary chemoreceptor cells in the nasal cavity serve as sentinels of respiration. *Proc. Natl. Acad. Sci. USA* 100:8981–86
56. Frank ME, Bouverat BP, MacKinnon BI, Hettinger TP. 2004. The distinctiveness of ionic and nonionic bitter stimuli. *Physiol. Behav.* 80:421–31
57. Frank ME, Wada Y, Makino J, Mizutani M, Umezawa H, et al. 2004. Variation in intake of sweet and bitter solutions by inbred strains of golden hamsters. *Behav. Genet.* 34:465–76
58. Fredriksson R, Lagerstrom MC, Lundin LG, Schioth HB. 2003. The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogon groups, and fingerprints. *Mol. Pharmacol.* 63:1256–72

59. Fukuwatari T, Kawada T, Tsuruta M, Hiraoka T, Iwanaga T, et al. 1997. Expression of the putative membrane fatty acid transporter (FAT) in taste buds of the circumvallate papillae in rats. *FEBS Lett.* 414:461–64
60. Fuller JL. 1974. Single-locus control of saccharin preference in mice. *J. Heredity* 65:33–36
61. Galindo-Cuspinera V, Winnig M, Bufe B, Meyerhof W, Breslin PA. 2006. A TAS1R receptor-based explanation of sweet "water-taste." *Nature* 441:354–57
62. Gilbertson TA, Baquero AF, Spray-Watson KJ. 2006. Water taste: the importance of osmotic sensing in the oral cavity. *J. Water Health* 4(Suppl. 1):35–40
63. Gilbertson TA, Fontenot DT, Liu L, Zhang H, Monroe WT. 1997. Fatty acid modulation of K+ channels in taste receptor cells: gustatory cues for dietary fat. *Am. J. Physiol.* 272:C1203–10
64. Gilbertson TA, Kim I, Siears NL, Zhang H, Liu L. 1999. The water response in taste cells: expression of aquaporin-1, -2 and -5 and the characterization of hypoosmic-induced currents in mammalian taste cells. *Chem. Senses* 24:596 (Abstr.)
65. Glendinning JI. 1994. Is the bitter rejection response always adaptive? *Physiol. Behav.* 56:1217–27
66. Harder DB, Capeless CG, Maggio JC, Boughter JD, Gannon KS, et al. 1992. Intermediate sucrose octa-acetate sensitivity suggests a third allele at mouse bitter taste locus *Soa* and *Soa-Rua* identity. *Chem. Senses* 17:391–401
67. Harder DB, Whitney G. 1985. Evidence for a third allele at the Soa locus controlling sucrose octaacetate tasting in mice. *Behav. Genet.* 15:594
68. Harder DB, Whitney G. 1998. A common polygenic basis for quinine and PROP avoidance in mice. *Chem. Senses* 23:327–32
69. Hinrichs AL, Wang JC, Bufe B, Kwon JM, Budde J, et al. 2006. Functional variant in a bitter-taste receptor (hTAS2R16) influences risk of alcohol dependence. *Am. J. Hum. Genet.* 78:103–11
70. Hiyama TY, Watanabe E, Ono K, Inenaga K, Tamkun MM, et al. 2002. Na(x) channel involved in CNS sodium-level sensing. *Nat. Neurosci.* 5:511–12
71. Hoon MA, Adler E, Lindemeier J, Battey JF, Ryba NJ, Zuker CS. 1999. Putative mammalian taste receptors: a class of taste-specific GPCRs with distinct topographic selectivity. *Cell* 96:541–51
72. Hoon MA, Ryba NJP. 1997. Analysis and comparison of partial sequences of clones from a taste-bud-enriched cDNA library. *J. Dental Res.* 76:831–38
73. Huang AL, Chen X, Hoon MA, Chandrashekar J, Guo W, et al. 2006. The cells and logic for mammalian sour taste detection. *Nature* 442:934–38
74. Inoue M, Beauchamp GK, Bachmanov AA. 2004. Gustatory neural responses to umami taste stimuli in C57BL/6ByJ and 129P3/J mice. *Chem. Senses* 29:789–95
75. Inoue M, Glendinning JI, Theodorides ML, Harkness S, Li X, et al. 2007. Allelic variation of the *Tas1r3* taste receptor gene selectively affects taste responses to sweeteners: evidence from 129.B6-*Tas1r3* congenic mice. Submitted
76. Inoue M, Li X, McCaughey SA, Beauchamp GK, Bachmanov AA. 2001. *Soa* genotype selectively affects mouse gustatory neural responses to sucrose octaacetate. *Physiol. Genom.* 5:181–86
77. Inoue M, McCaughey SA, Bachmanov AA, Beauchamp GK. 2001. Whole-nerve chorda tympani responses to sweeteners in C57BL/6ByJ and 129P3/J mice. *Chem. Senses* 26:915–23
78. Inoue M, Reed DR, Li X, Tordoff MG, Beauchamp GK, Bachmanov AA. 2004. Allelic variation of the *Tas1r3* taste receptor gene selectively affects behavioral and neural taste

responses to sweeteners in the F_2 hybrids between C57BL/6ByJ and 129P3/J mice. *J. Neurosci.* 24:2296–303

79. Ishimaru Y, Inada H, Kubota M, Zhuang H, Tominaga M, Matsunami H. 2006. Transient receptor potential family members PKD1L3 and PKD2L1 form a candidate sour taste receptor. *Proc. Natl. Acad. Sci. USA* 103:12569–74
80. Jiang P, Cui M, Ji Q, Snyder L, Liu Z, et al. 2005. Molecular mechanisms of sweet receptor function. *Chem. Senses* 30(Suppl. 1):i17–18
81. Jiang P, Cui M, Zhao B, Liu Z, Snyder LA, et al. 2005. Lactisole interacts with the transmembrane domains of human T1R3 to inhibit sweet taste. *J. Biol. Chem.* 280:15238–46
82. Jiang P, Cui M, Zhao B, Snyder LA, Benard LM, et al. 2005. Identification of the cyclamate interaction site within the transmembrane domain of the human sweet taste receptor subunit T1R3. *J. Biol. Chem.* 280:34296–305
83. Jiang P, Ji Q, Liu Z, Snyder LA, Benard LM, et al. 2004. The cysteine-rich region of T1R3 determines responses to intensely sweet proteins. *J. Biol. Chem.* 279:45068–75
84. Kampov-Polevoy AB, Eick C, Boland G, Khalitov E, Crews FT. 2004. Sweet liking, novelty seeking, and gender predict alcoholic status. *Alcohol. Clin. Exp. Res.* 28:1291–98
85. Kellenberger S, Schild L. 2002. Epithelial sodium channel/degenerin family of ion channels: a variety of functions for a shared structure. *Physiol. Rev.* 82:735–67
86. Kim MR, Kusakabe Y, Miura H, Shindo Y, Ninomiya Y, Hino A. 2003. Regional expression patterns of taste receptors and gustducin in the mouse tongue. *Biochem. Biophys. Res. Commun.* 312:500–6
87. Kim U, Wooding S, Ricci D, Jorde LB, Drayna D. 2005. Worldwide haplotype diversity and coding sequence variation at human bitter taste receptor loci. *Hum. Mutat.* 26:199–204
88. Kim UK, Jorgenson E, Coon H, Leppert M, Risch N, Drayna D. 2003. Positional cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide. *Science* 299:1221–25
89. Kim UK, Wooding S, Riaz N, Jorde LB, Drayna D. 2006. Variation in the human TAS1R taste receptor genes. *Chem. Senses* 31:599–611
90. Kinnamon SC, Price MP, Stone LM, Lin W, Welsh MJ. 2000. The acid sensing ion channel BNC1 is not required for sour taste transduction. *13th Internat. Symp. Olfact. Taste* XIII:80 (Abstr.)
91. Kitagawa M, Kusakabe Y, Miura H, Ninomiya Y, Hino A. 2001. Molecular genetic identification of a candidate receptor gene for sweet taste. *Biochem. Biophys. Res. Commun.* 283:236–42
92. Kiuchi S, Yamada T, Kiyokawa N, Saito T, Fujimoto J, Yasue H. 2006. Genomic structure of swine taste receptor family 1 member 3, TAS1R3, and its expression in tissues. *Cytogenet. Genome Res.* 115:51–61
93. Kuhn C, Bufe B, Winnig M, Hofmann T, Frank O, et al. 2004. Bitter taste receptors for saccharin and acesulfame K. *J. Neurosci.* 24:10260–65
94. Laugerette F, Passilly-Degrace P, Patris B, Niot I, Febbraio M, et al. 2005. CD36 involvement in orosensory detection of dietary lipids, spontaneous fat preference, and digestive secretions. *J. Clin. Invest.* 115:3177–84
95. Le Roy I, Pager J, Roubertoux PL. 1999. Genetic dissection of gustatory sensitivity to bitterness (sucrose octaacetate) in mice. *CR Acad. Sci. III* 322:831–36
96. Levin BE, Routh VH, Kang L, Sanders NM, Dunn-Meynell AA. 2004. Neuronal glucosensing: What do we know after 50 years? *Diabetes* 53:2521–28

97. Li X, Bachmanov AA, Li S, Chen Z, Tordoff MG, et al. 2002. Genetic, physical and comparative map of the subtelomeric region of mouse chromosome 4. *Mamm. Genome* 13:5–19
98. Li X, Inoue M, Reed DR, Huque T, Puchalski RB, et al. 2001. High-resolution genetic mapping of the saccharin preference locus (*Sac*) and the putative sweet taste receptor (T1R1) gene (*Gpr70*) to mouse distal chromosome 4. *Mamm. Genome* 12:13–16
99. Li X, Li W, Wang H, Cao J, Maehashi K, et al. 2005. Pseudogenization of a sweet-receptor gene accounts for cats' indifference toward sugar. *PLoS Genet.* 1:27–35
100. Li X, Staszewski L, Xu H, Durick K, Zoller M, Adler E. 2002. Human receptors for sweet and umami taste. *Proc. Natl. Acad. Sci. USA* 99:4692–96
101. Liao J, Schultz PG. 2003. Three sweet receptor genes are clustered in human chromosome 1. *Mamm. Genome* 14:291–301
102. Lin W, Ogura T, Kinnamon SC. 2002. Acid-activated cation currents in rat vallate taste receptor cells. *J. Neurophysiol.* 88:133–41
103. Lindemann B. 1997. Sodium taste. *Curr. Opin. Nephrol. Hypertens.* 6:425–29
104. Liu L, Leonard AS, Motto DG, Feller MA, Price MP, et al. 2003. Contribution of *Drosophila* DEG/ENaC genes to salt taste. *Neuron* 39:133–46
105. Liu L, Simon SA. 2001. Acidic stimuli activates two distinct pathways in taste receptor cells from rat fungiform papillae. *Brain Res.* 923:58–70
106. LopezJimenez ND, Cavenagh MM, Sainz E, Cruz-Ithier MA, Battey JF, Sullivan SL. 2006. Two members of the TRPP family of ion channels, Pkd1l3 and Pkd2l1, are co-expressed in a subset of taste receptor cells. *J. Neurochem.* 98:68–77
107. Lu K, McDaniel AH, Tordoff MG, Li X, Beauchamp GK, et al. 2005. No relationship between sequence variation in protein coding regions of the *Tas1r3* gene and saccharin preference in rats. *Chem. Senses* 30:231–40
108. Lush IE. 1981. The genetics of tasting in mice. I. Sucrose octaacetate. *Genet. Res.* 38:93–95
109. Lush IE. 1982. The genetics of tasting in mice. II. Strychnine. *Chem. Senses* 7:93–98
110. Lush IE. 1984. The genetics of tasting in mice. III. Quinine. *Genet. Res.* 44:151–60
111. Lush IE. 1986. Differences between mouse strains in their consumption of phenylthiourea (PTC). *Heredity* 57:319–23
112. Lush IE. 1986. The genetics of tasting in mice. IV. The acetates of raffinose, galactose and b-lactose. *Genet. Res.* 47:117–23
113. Lush IE. 1989. The genetics of tasting in mice. VI. Saccharin, acesulfame, dulcin and sucrose. *Genet. Res.* 53:95–99
114. Lush IE, Holland G. 1988. The genetics of tasting in mice. V. Glycine and cycloheximide. *Genet. Res.* 52:207–12
115. Lush IE, Hornigold N, King P, Stoye JP. 1995. The genetics of tasting in mice. VII. Glycine revisited, and the chromosomal location of *Sac* and *Soa*. *Genet. Res.* 66:167–74
116. Lyall V, Alam RI, Phan DQ, Ereso GL, Phan TH, et al. 2001. Decrease in rat taste receptor cell intracellular pH is the proximate stimulus in sour taste transduction. *Am. J. Physiol. Cell Physiol.* 281:C1005–13
117. Lyall V, Heck GL, Vinnikova AK, Ghosh S, Phan TH, et al. 2004. The mammalian amiloride-insensitive nonspecific salt taste receptor is a vanilloid receptor-1 variant. *J. Physiol.* 558:147–59
118. Matsunami H, Montmayeur JP, Buck LB. 2000. A family of candidate taste receptors in human and mouse. *Nature* 404:601–4
119. Mattes RD. 2005. Fat taste and lipid metabolism in humans. *Physiol. Behav.* 86:691–97

120. Max M, Shanker YG, Huang L, Rong M, Liu Z, et al. 2001. *Tas1r3*, encoding a new candidate taste receptor, is allelic to the sweet responsiveness locus *Sac*. *Nat. Genet.* 28:58–63
121. Mennella JA, Pepino MY, Reed DR. 2005. Genetic and environmental determinants of bitter perception and sweet preferences. *Pediatrics* 115:e216–22
122. Meyerhof W. 2005. Elucidation of mammalian bitter taste. *Rev. Physiol. Biochem. Pharmacol.* 154:37–72
123. Montmayeur JP, Liberles SD, Matsunami H, Buck LB. 2001. A candidate taste receptor gene near a sweet taste locus. *Nat. Neurosci.* 4:492–98
124. Mueller KL, Hoon MA, Erlenbach I, Chandrashekar J, Zuker CS, Ryba NJ. 2005. The receptors and coding logic for bitter taste. *Nature* 434:225–29
125. Naim M, Nir S, Spielman AI, Noble AC, Peri I, et al. 2002. Hypothesis of receptor-dependent and receptor-independent mechanisms for bitter and sweet taste transduction: implications for slow taste onset and lingering aftertaste. In *Chemistry of Taste: Mechanisms, Behaviors, and Mimics. ACS Symposium Series; 825*, ed. P Given, D Parades, pp. 2–17. Washington, DC: Am. Chem. Soc.
126. Nelson G, Chandrashekar J, Hoon MA, Feng L, Zhao G, et al. 2002. An amino-acid taste receptor. *Nature* 416:199–202
127. Nelson G, Hoon MA, Chandrashekar J, Zhang Y, Ryba NJ, Zuker CS. 2001. Mammalian sweet taste receptors. *Cell* 106:381–90
128. Nelson TM, Munger SD, Boughter JD Jr. 2003. Taste sensitivities to PROP and PTC vary independently in mice. *Chem. Senses* 28:695–704
129. Nelson TM, Munger SD, Boughter JD Jr. 2005. Haplotypes at the Tas2r locus on distal chromosome 6 vary with quinine taste sensitivity in inbred mice. *BMC Genet.* 6:32
130. Nie Y, Vigues S, Hobbs JR, Conn GL, Munger SD. 2005. Distinct contributions of T1R2 and T1R3 taste receptor subunits to the detection of sweet stimuli. *Curr. Biol.* 15:1948–52
131. Ninomiya Y, Kajiura H, Mochizuki K. 1993. Differential taste responses of mouse chorda tympani and glossopharyngeal nerves to sugars and amino acids. *Neurosci. Lett.* 163:197–200
132. Ninomiya Y, Nakashima K, Fukuda A, Nishino H, Sugimura T, et al. 2000. Responses to umami substances in taste bud cells innervated by the chorda tympani and glossopharyngeal nerves. *J. Nutr.* 130:950–53S
133. Phillips TJ, Crabbe JC, Metten P, Belknap JK. 1994. Localization of genes affecting alcohol drinking in mice. *Alcohol. Clin. Exp. Res.* 18:931–41
134. Pin JP, Galvez T, Prezeau L. 2003. Evolution, structure, and activation mechanism of family 3/C G-protein-coupled receptors. *Pharmacol. Ther.* 98:325–54
135. Prodi DA, Drayna D, Forabosco P, Palmas MA, Maestrale GB, et al. 2004. Bitter taste study in a sardinian genetic isolate supports the association of phenylthiocarbamide sensitivity to the TAS2R38 bitter receptor gene. *Chem. Senses* 29:697–702
136. Ramirez I. 1992. Chemoreception for fat: Do rats sense triglycerides directly? *Appetite* 18:193–206
137. Reed DR, Li S, Li X, Huang L, Tordoff MG, et al. 2004. Polymorphisms in the taste receptor gene (*Tas1r3*) region are associated with saccharin preference in 30 mouse strains. *J. Neurosci.* 24:938–46
138. Reed DR, McDaniel AH. 2006. The human sweet tooth. *BMC Oral Health* 6(Suppl. 1):S17

139. Reed DR, Nanthakumar E, North M, Bell C, Bartoshuk LM, Price RA. 1999. Localization of a gene for bitter-taste perception to human chromosome 5p15. *Am. J. Hum. Genet.* 64:1478–80
140. Reed DR, Tanaka T, McDaniel AH. 2006. Diverse tastes: genetics of sweet and bitter perception. *Physiol. Behav.* 88:215–26
141. Richter TA, Caicedo A, Roper SD. 2003. Sour taste stimuli evoke Ca2+ and pH responses in mouse taste cells. *J. Physiol.* 547:475–83
142. Richter TA, Dvoryanchikov GA, Chaudhari N, Roper SD. 2004. Acid-sensitive two-pore domain potassium (K2P) channels in mouse taste buds. *J. Neurophysiol.* 92:1928–36
143. Richter TA, Dvoryanchikov GA, Roper SD, Chaudhari N. 2004. Acid-sensing ion channel-2 is not necessary for sour taste in mice. *J. Neurosci.* 24:4088–91
144. Rolls ET, Scott TR. 2003. Central taste anatomy and neurophysiology. In *Handbook of Olfaction and Gustation*, ed. RL Doty, pp. 679–705. New York: Marcel Dekker
145. Rosenzweig S, Yan W, Dasso M, Spielman AI. 1999. Possible novel mechanism for bitter taste mediated through cGMP. *J. Neurophysiol.* 81:1661–65
146. Rozengurt N, Wu SV, Chen MC, Huang C, Sternini C, Rozengurt E. 2006. Colocalization of the alpha-subunit of gustducin with PYY and GLP-1 in L cells of human colon. *Am. J. Physiol. Gastrointest. Liver Physiol.* 291:G792–802
147. Sainz E, Korley JN, Battey JF, Sullivan SL. 2001. Identification of a novel member of the T1R family of putative taste receptors. *J. Neurochem.* 77:896–903
148. San Gabriel A, Uneyama H, Yoshie S, Torii K. 2005. Cloning and characterization of a novel mGluR1 variant from vallate papillae that functions as a receptor for L-glutamate stimuli. *Chem. Senses* 30(Suppl. 1):i25–26
149. Sandell MA, Breslin PA. 2006. Variability in a taste-receptor gene determines whether we taste toxins in food. *Curr. Biol.* 16:R792–94
150. Sawano S, Seto E, Mori T, Hayashi Y. 2005. G-protein-dependent and -independent pathways in denatonium signal transduction. *Biosci. Biotechnol. Biochem.* 69:1643–51
151. Sclafani A. 2004. The sixth taste? *Appetite* 43:1–3
152. Scott TR, Giza BK, Yan J. 1999. Gustatory neural coding in the cortex of the alert cynomolgus macaque: the quality of bitterness. *J. Neurophysiol.* 81:60–71
153. Soranzo N, Bufe B, Sabeti PC, Wilson JF, Weale ME, et al. 2005. Positive selection on a high-sensitivity allele of the human bitter-taste receptor TAS2R16. *Curr. Biol.* 15:1257–65
154. Spector AC, Kopka SL. 2002. Rats fail to discriminate quinine from denatonium: implications for the neural coding of bitter-tasting compounds. *J. Neurosci.* 22:1937–41
155. Sternini C. 2007. Taste receptors in the gastrointestinal tract. IV. Functional implications of bitter taste receptors in gastrointestinal chemosensing. *Am. J. Physiol. Gastrointest. Liver Physiol.* 292:G457–61
156. Stevens DR, Seifert R, Bufe B, Muller F, Kremmer E, et al. 2001. Hyperpolarization-activated channels HCN1 and HCN4 mediate responses to sour stimuli. *Nature* 413:631–35
157. Tamames J, Valencia A. 2006. The success (or not) of HUGO nomenclature. *Genome Biol.* 7:402
158. Taniguchi K. 2004. Expression of the sweet receptor protein, T1R3, in the human liver and pancreas. *J. Vet. Med. Sci.* 66:1311–14
159. Tobach E, Bellin JS, Das DK. 1974. Differences in bitter taste perception in three strains of rats. *Behav. Genet.* 4:405–10

160. Toyono T, Seta Y, Kataoka S, Kawano S, Shigemoto R, Toyoshima K. 2003. Expression of metabotropic glutamate receptor group I in rat gustatory papillae. *Cell Tissue Res.* 313:29–35
161. Ueda T, Ugawa S, Ishida Y, Shibata Y, Murakami S, Shimada S. 2001. Identification of coding single-nucleotide polymorphisms in human taste receptor genes involving bitter tasting. *Biochem. Biophys. Res. Commun.* 285:147–51
162. Ugawa S. 2003. Identification of sour-taste receptor genes. *Anat. Sci. Int.* 78:205–10
163. Ugawa S, Minami Y, Guo W, Saishin Y, Takatsuji K, et al. 1998. Receptor that leaves a sour taste in the mouth. *Nature* 395:555–56
164. Ugawa S, Yamamoto T, Ueda T, Ishida Y, Inagaki A, et al. 2003. Amiloride-insensitive currents of the acid-sensing ion channel-2a (ASIC2a)/ASIC2b heteromeric sour-taste receptor channel. *J. Neurosci.* 23:3616–22
165. Vinnikova AK, Alam RI, Malik SA, Ereso GL, Feldman GM, et al. 2004. Na+-H+ exchange activity in taste receptor cells. *J. Neurophysiol.* 91:1297–313
166. Waldmann R, Lazdunski M. 1998. H(+)-gated cation channels: neuronal acid sensors in the NaC/DEG family of ion channels. *Curr. Opin. Neurobiol.* 8:418–24
167. Wang X, Thomas SD, Zhang J. 2004. Relaxation of selective constraint and loss of function in the evolution of human bitter taste receptor genes. *Hum. Mol. Genet.* 13:2671–78
168. Whitney G, Harder DB. 1986. Single locus control of sucrose octaacetate tasting among mice. *Behav. Genet.* 16:559–74
169. Winnig M, Bufe B, Meyerhof W. 2005. Valine 738 and lysine 735 in the fifth transmembrane domain of rTas1r3 mediate insensitivity towards lactisole of the rat sweet taste receptor. *BMC Neurosci.* 6:22
170. Witt M, Reutter K, Miller IJ. 2003. Morphology of peripheral taste system. In *Handbook of Olfaction and Gustation*, ed. RL Doty, pp. 651–77. New York: Marcel Dekker
171. Wong GT, Gannon KS, Margolskee RF. 1996. Transduction of bitter and sweet taste by gustducin. *Nature* 381:796–800
172. Wooding S, Bufe B, Grassi C, Howard MT, Stone AC, et al. 2006. Independent evolution of bitter-taste sensitivity in humans and chimpanzees. *Nature* 440:930–34
173. Wooding S, Kim UK, Bamshad MJ, Larsen J, Jorde LB, Drayna D. 2004. Natural selection and molecular evolution in PTC, a bitter-taste receptor gene. *Am. J. Hum. Genet.* 74:637–46
174. Wu SV, Chen MC, Rozengurt E. 2005. Genomic organization, expression, and function of bitter taste receptors (T2R) in mouse and rat. *Physiol. Genomics* 22:139–49
175. Wu SV, Rozengurt N, Yang M, Young SH, Sinnett-Smith J, Rozengurt E. 2002. Expression of bitter taste receptors of the T2R family in the gastrointestinal tract and enteroendocrine STC-1 cells. *Proc. Natl. Acad. Sci. USA* 99:2392–97
176. Xu H, Staszewski L, Tang H, Adler E, Zoller M, Li X. 2004. Different functional roles of T1R subunits in the heteromeric taste receptors. *Proc. Natl. Acad. Sci. USA* 101:14258–63
177. Zhang X, Fitzsimmons RL, Cleland LG, Ey PL, Zannettino AC, et al. 2003. CD36/fatty acid translocase in rats: distribution, isolation from hepatocytes, and comparison with the scavenger receptor SR-B1. *Lab Invest.* 83:317–32
178. Zhang Y, Hoon MA, Chandrashekar J, Mueller KL, Cook B, et al. 2003. Coding of sweet, bitter, and umami tastes. Different receptor cells sharing similar signaling pathways. *Cell* 112:293–301
179. Zhao GQ, Zhang Y, Hoon MA, Chandrashekar J, Erlenbach I, et al. 2003. The receptors for mammalian sweet and umami taste. *Cell* 115:255–66

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