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Genetics of Taste Receptors

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Abstract

Taste receptors function as one of the interfaces between internal and external milieus. Taste receptors for sweet and umami (T1R [taste receptor, type 1]), bitter (T2R [taste receptor, type 2]), and salty (ENaC [epithelial sodium channel]) have been discovered in the recent years, but transduction mechanisms of sour taste and ENaC-independent salt taste are still poorly understood. In addition to these five main taste qualities, the taste system detects such noncanonical “tastes” as water, fat, and complex carbohydrates, but their reception mechanisms require further research. Variations in taste receptor genes between and within vertebrate species contribute to individual and species differences in taste-related behaviors. These variations are shaped by evolutionary forces and reflect species adaptations to their chemical environments and feeding ecology. Principles of drug discovery can be applied to taste receptors as targets in order to develop novel taste compounds to satisfy demand in better artificial sweeteners, enhancers of sugar and sodium taste, and blockers of bitterness of food ingredients and oral medications.

Keywords

Gustatory; sweet; bitter; umami; salty; sour; receptor; gene

INTRODUCTION

This review focuses on genetics of taste receptors in vertebrate animals, specifically, how gene structure and variation influence expression and function of taste receptors, and how this affects taste function. We describe the different taste qualities and discuss two main types of genetic variation: variation among orthologous genes in different vertebrate species, and variation of alleles within species. Although environment can also affect expression of taste receptor genes through physiological and epigenetic mechanisms, this is outside the scope of this review. For information on invertebrate taste receptors, see, e.g., [1, 2]; for other aspects of taste genetics, including genetics of taste perception, see, e.g., [3–7]).

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

Taste System and Taste Receptors

In mammals, the gustatory system comprises taste cells, afferent gustatory nerves, and brain structures involved in central processing of taste. The taste cascade begins with taste receptor cells organized in taste buds, most of which are located within gustatory papillae in the tongue. Taste bud cells come in four types: type I, II, and III cells and basal cells. Types I–III are mature taste receptor cells exposed to the oral cavity to interact with taste stimuli via taste receptor proteins. This interaction results in excitation that is transmitted via afferent gustatory nerves to the brain to evoke taste perception. Taste perception has several aspects: intensity, hedonics (pleasantness or unpleasantness), and quality. Five taste qualities are known to be perceived by humans and many nonhuman mammals: sweet, umami, bitter, salty, and sour. The existence of distinct taste qualities implies that each has a specific coding mechanism mediated by specialized taste receptors. Discovery of receptors for bitter, sweet, umami, and salty taste (Fig. 1) has supported this notion.

Although several proteins have been suggested to function as taste receptors, not all of them have been unanimously accepted as such. Several requirements need to be met to affirm that a molecule functions as a taste receptor: (1) known molecular identity (DNA, RNA, and protein sequences); (2) expression in taste receptor cells; (3) interaction with appropriate ligands; and (4) changes in taste responsiveness as a result of experimentally altered receptors. All these criteria have been met for taste receptors for sweet and umami (T1R [taste receptor, type 1]), bitter (T2R [taste receptor, type 2]), and salty (ENaC [epithelial sodium channel]) taste (Fig. 1), but sour taste receptors are still unknown (although several candidates have been proposed).

Between-species Variation and Evolution of Taste Receptors

T1Rs, T2Rs, and ENaCs are conserved among vertebrates. Their respective genes and proteins are considered orthologs, because their sequence similarity suggests that they originated from common ancestral genes. The order of chromosomal location of orthologous taste receptor genes is also conserved among different species (providing an example of conserved synteny). Despite this conservation, vertebrate species differ in both sequence and numbers of receptor genes. Gene duplications, deletions, and pseudogenization contribute to species variation in gene number.

This interspecies variation has been shaped by evolutionary forces, likely reflecting adaptation to differences in their diets. The survival of all animals depends on consumption of nutrients, and taste guides animals in choosing food that is safe to consume and appropriate for bodily needs. Many of the same nutrients (e.g., sugars, amino acids, salts) are consumed by different species, yet many species have very different diets (e.g., herbivores and carnivores). Sources of nutrients may contain toxic substances, and each species may be exposed to different sets of toxins in their diets. Covariation between taste receptors and diet suggests that during the evolution the taste system adjusted to support the dietary needs of individual species.

Within-species Variation of Taste Receptors

Allelic variation of taste receptor genes is most documented in humans and mice. Naturally occurring polymorphisms contribute to individual variation in taste responses in both species. Such allelic variation can affect food perception, choice, and consumption and thus can influence nutrition and predispose to certain diseases. In mice, in addition to naturally occurring polymorphisms, mutant alleles of taste receptor genes have been produced by targeted mutagenesis. Associations of taste receptor variants with changes in responsiveness to taste stimuli provide a tool to study receptor-ligand interactions [8].

Pharmaceutical Design and Taste Receptors

There is a growing interest in developing novel taste stimuli and taste modifiers for humans and other animals. For humans, areas of interest include making foods and drinks healthier without sacrificing their palatability, and making oral medications more acceptable to patients. There is a demand 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 improving palatability 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 molecular identity of the taste receptors.

Discovery of most of the mammalian taste receptors in the last decade allowed scientists to apply principles of drug discovery and to use taste receptors as targets to develop novel taste stimuli, enhancers, and blockers (see, e.g., [9–11]). Growing knowledge about within- and between-species variation in taste receptors will help to tailor these products to target consumers. Recent findings of expression of taste receptors in internal organs (e.g., airway epithelia, gut, pancreas, and testes) and accumulating data that they play a role in internal chemoreception (e.g., [12–15]) also open possibilities for using taste receptors to develop drugs for treating diseases associated with these organs.

SWEET AND UMAMI TASTE

Sugars are the most common natural taste stimuli that humans describe as sweet and are innately attractive to many animals [16–18]. A wide range of other chemicals taste sweet to humans (e.g., some sugar alcohols, glycosides, amino acids, and proteins [19, 20]). Many of these compounds also evoke sucrose-like qualitative taste sensation and appetitive consummatory behavior in nonhuman mammals. In contrast to sweet taste, which humans universally appreciate, umami is lesser known. Most languages have only four words for basic taste qualities: sweet, salty, sour, and bitter. The word *umami* was first used around 1908 by a Japanese chemist, Dr. Kikunae Ikeda [21]. He discovered that glutamic acid and its salts evoke a taste sensation distinct from the four known taste qualities. To describe this additional basic taste quality, he combined Japanese words *umai* (旨い; “delicious” or “savory”) and *mi* (味; “taste”) to derive a new word, *umami* (旨味 in kanji, or うま味 in a mixed hiragana-kanji spelling). In English, umami taste sometimes is described as “savory taste” or “glutamate taste” [22].

Umami-tasting compounds include some L-amino acids (e.g., glutamate and aspartate), purine 5′-ribonucleotides, theogallin, theanine, ibotenic, tricholomic, succinic, and gallic acids, and several peptides. The 5′-ribonucleotides potentiate taste of L-glutamate. Many of these compounds have other chemosensory components, in addition to umami taste. For example, in monosodium glutamate (MSG), the anion (L-glutamate) generates an umami taste, and the cation (Na^+) contributes a salty taste. A good way to experience umami is to compare tastes of equimolar solutions of MSG and NaCl. Both solutions have saltiness, which is attributed to sodium, but MSG also has another taste component not present in NaCl solutions—umami. There is also strong evidence that umami taste stimuli evoke a unique (glutamate-like) taste in nonhuman animals [23–25].

Sweet and Umami Taste Receptors

G protein-coupled receptor (GPCR) proteins from the T1R family (Fig. 1a) play a central role in reception of sweet and umami taste in humans (and sucrose- and glutamate-like taste in nonhuman animals). A T1R2+3 heterodimer functions as a sweet taste receptor [26, 27] responding to a broad variety of ligands in both humans and rodents. T1R3 alone may function as a receptor for high sucrose concentrations [28]. A T1R1+3 heterodimer functions as an umami taste receptor in humans [27] and is a more broadly tuned L-amino acid taste receptor in mice and fish [29, 262], although multiple combinations of T1R2 with T1R3 also function as L-amino acid receptors in fish [262].

Depending on GPCR classification system, T1Rs belong to class C (metabotropic glutamate/pheromone) family [30–32] or the glutamate family [33]. In humans and many mammalian species, this family includes three proteins: T1R1, T1R2 and T1R3. Their corresponding gene names are taste receptor, type 1, members 1, 2, and 3, respectively, with gene symbols *TAS1R1*, *TAS1R2*, and *TAS1R3* in humans and *Tas1r1*, *Tas1r2*, and *Tas1r3* in other species. Numbers of T1R genes vary in some species (described below). The three human *TAS1R* genes are located in the short arm of human chromosome 1 (1p36) in the order *TAS1R2—TAS1R1—TAS1R3*. Their mouse orthologs reside in a region of conserved synteny in distal chromosome 4 in the same order: *Tas1r2—Tas1r1—Tas1r3*. The mouse *Tas1r* genes contain six coding exons that are translated into proteins of 842–858 amino acids. The T1R proteins 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 (see Fig. 1a).

T1Rs are expressed in type II taste bud cells. T1R3 is co-expressed in the same taste cells with either T1R1 or T1R2 [26, 34, 35, 63], but some taste cells express only T1R3 in mammal [26] and only T1R2s in fish [63]. This co-expression of T1Rs is consistent with their function as heterodimers (T1R1+3 and T1R2+3). Mice with targeted mutations of the T1R genes have diminished taste responses to sweet and/or umami taste stimuli [28, 36].

Data on T1R ligand specificity in mammals suggest that T1R1+3 and T1R2+3 are the main umami and sweet receptors, respectively, although T1R1 was recently demonstrated to be involved in sweet reception [263]. However, there is evidence for additional reception mechanisms for sweet or umami taste. They include glucose transporters and metabolic

sensors, which may be involved in sugar tasting [37], and the ability of some sweeteners to penetrate the membrane of the taste bud cells and interact with in-tracellular targets [38–40]. Splice variants of metabotropic glutamate receptors mGluR4 and mGluR1 and the N-methyl-D-aspartate (NMDA)-type glutamate ion channel receptor (all of which are involved in glutamatergic synaptic transmission in the brain) have been proposed as candidate mammalian taste receptors for umami or glutamate taste [41–48]. Purine 5′-nucleotides may activate different taste receptors than glutamate in rats [49]. Catfish (*Ictalurus punctatus*) taste receptors for some L-amino acids behave as ligand-gated ion channel receptors [50–53], and combinations of T1R2+3 function as L-amino acid receptors in medaka fish (*Olyzias latipes*) and zebrafish (*Danio rerio*) [262].

Between-Species Variation of Sweet and Umami Taste Receptors

Two main processes have shaped repertoires of T1Rs in different species and their responsiveness to sweet and umami taste stimuli. First, pseudogenization and duplication changed numbers of T1R family members; pseudogenization is responsible for sweet or umami taste “blindness” in some species. Second, sequence variants within functional T1Rs resulted in species-specific differences in receptor-ligand interactions. Although ligands for the T1R receptors have been experimentally confirmed for only a few species (mostly humans and rodents, but fish T1Rs were shown to function as amino acid receptors [262]), it is likely that their orthologs in other species have similar ligand specificities. Therefore, species differences in sweet and umami taste preferences [54–62] are expected to be due to variation in the T1R genes.

Although many mammals have three T1R genes coding T1R1, T1R2, and T1R3, as described above, numbers of functional T1R genes in other vertebrate species range from complete absence in the western clawed frog, vampire bats, sea lion, and bottlenose dolphin to five in some species of fish (Table 1). Several fish species have two or three T1R2 genes, suggesting that T1R expansion in fish is probably due to duplication of *Tas1r2* [63, 64].

Several species have one or more pseudogenized T1R genes. *Tas1r1*, which codes part of the umami heterodimer, is a pseudogene in the giant panda [65–67] and six pinnipeds (suborder Caniformia): spotted seal, harbor seal, Caspian seal, northern elephant seal, Australian sea lion, and South American sea lion [67]. *Tas1r1* is absent, unamplifiable, or pseudogenized in all 31 species of bats examined [68]. These mutations deem the umami/amino acid taste receptor dimer T1R1+3 nonfunctional in these species. Most species of the order Carnivora have intact *Tas1r1* and have either carnivorous or omnivorous feeding strategies. While the giant panda is also a carnivoran, unlike the other species of this order its diet is almost exclusively vegetarian (bamboo). The *Tas1r1* pseudogenization was likely associated with evolution of feeding behavior in the giant panda because the estimated date of its dietary switch to bamboo coincides with the date of its *Tas1r1* pseudogenization [65]. The six pinniped species examined are strictly carnivorous [67], and bats examined include fruit, insect, and blood feeders [68], so widespread *Tas1r1* pseudogenization in these clades is puzzling.

The *Tas1r2* gene, which codes part of the sweet heterodimer, is absent in the genomes of the chicken [64, 69, 70], zebra finch [70], and horse [70] (but see [71]). *Tas1r2* is a pseudogene

in four Felidae species (domestic cat, tiger, cheetah, and Asiatic lion [59, 72]) and six nonfeline species from suborders Feliformia (spotted hyena, fossa, and banded linsang) and Caniformia (southern fur seal, Pacific harbor seal, and Asian small-clawed otter) [73]. These mutations result in a nonfunctional T1R2+3 heterodimeric sweet taste receptor and explain the lack of attraction to sugars and other sweeteners documented at least in some of these species [54–59, 73]. All these animals are either obligate carnivores or, in case of the chicken, granivores and do not seek sugars in their food. Thus, loss of the *Tas1r2* gene and lack of sweet taste responsiveness in these animals may be a consequence of their feeding behavior, which does not require a sweet taste receptor for proper food choice, leading to a lack of selective advantage of having a functional sweet taste receptor that recognizes sugars. Many other species of the order of Carnivora have a functional *Tas1r2* structure [59, 64, 72, 73] and are attracted to sugars [59, 73–75], including dogs, lesser panda, domestic ferret, Haussa genet, meerkat, yellow mongoose, aardwolf, Canadian otter, spectacled bear, raccoon, and red wolf. Some birds also recognize sugar taste [76–78], suggesting that they may have a functional T1R2, although this has not been confirmed experimentally.

All three T1R genes are lost in the tongueless western clawed frog [64], sea lion, bottlenose dolphin [73], and vampire bats [68, 70]. Consistent with this, common vampire bats (*Desmodus rotundus*) are indifferent to sweet stimuli but avoid salty, sour, and bitter tastes (umami taste was not evaluated) [79]. Taste function has not been evaluated in the other species, but lack of taste receptors may be related to their feeding behavior, which involves swallowing food whole without chewing (e.g., sea lion, dolphin) [73] or feeding exclusively on blood (vampire bats) [68]. Thus, pseudogenization and duplication of T1R genes occurred independently multiple times in different vertebrate lineages during evolution.

In addition to changes in number of T1R genes, their sequence variants are also responsible for species differences in sweet and umami taste. For example, several sweeteners (aspartame, cyclamate, neohesperidin dihydrochalcone, neotame, and sweet proteins) are perceived as sweet by humans but not by rodents (e.g., [80–82]). Correspondingly, human but not rodent T1R2+3 responds to these sweeteners. Heterologously expressed T1R1+3 functions as a broadly tuned L-amino acid receptor in mice and as a more narrowly tuned umami receptor in humans. The role that sequence variation between T1R orthologs plays in species differences in sweet and umami taste has been shown in studies using heterologously expressed interspecies T1R chimeras or receptors with species-specific site-directed mutations, and in genetically engineered mice expressing human receptors [26–29, 83–89]. One well-studied example of species differences in sweet taste is sensitivity to aspartame. Humans, apes, and old-world monkeys perceive aspartame as sweet, but other primate species and most nonprimate species do not [60]. Recent studies identified sequence variants of T1R2 and T1R3 that are associated with ability to taste aspartame and are predicted to influence aspartame binding to the T1R2+3 receptor [90, 91]. Results of all these studies suggest that evolutionary changes of T1R receptors can affect their ligand-binding properties.

Within-Species Variation of Sweet and Umami Taste Receptors

Within-species polymorphisms of the T1R genes were found in humans [92], rats [93], and mice [94], but only in humans and mice have they been found to be associated with sweet or umami taste responsiveness.

Humans differ in perception of sweet (reviewed in [95–100]) and umami [101] tastes. Non-amino acid-coding single-nucleotide polymorphisms (SNPs) in the *TAS1R3* promoter were found to be associated with taste sensitivity to sucrose in humans and to influence *TAS1R3* promoter activity *in vitro* [102]. Another study found association of a missense variant in *TAS1R2* with habitual consumption of sugars [103]. Polymorphisms in *TAS1R1* and *TAS1R3*, as well as a candidate umami receptor gene, *mGluR1*, partially explain variation in umami taste [104–106]

In mice, variation in sweetener preference is associated with the *Sac* (saccharin preference) locus [107–110]. Chromosomal mapping and positional cloning of the *Sac* locus have identified it as the *Tas1r3* gene [94, 111, 112], which was instrumental in discovery of the T1R taste receptors. Analyses of the *Tas1r3* sequence variants across multiple inbred strains identified a missense polymorphism (I60T) in the extracellular N-terminus of the T1R3 protein as a candidate causative variant for ligand binding and phenotypical variation in sweet taste [94]. The effect of this polymorphism on T1R3 ligand binding was confirmed *in vitro* [113]. *Tas1r3* polymorphisms affect behavioral and neural taste responses to many different sweeteners [114, 115], indicating that these sweeteners activate a taste receptor involving T1R3. However, *Tas1r3* genotype did not affect taste responses to several sweet-tasting amino acids (L-glutamine, L-threonine, L-alanine, glycine), glucose polymers (Polycose, maltooligosaccharide), or umami, salty, sour, or bitter taste stimuli [114, 115]. The T1R3 protein is involved in transduction of both sweet and umami tastes, and disruption of the *Tas1r3* gene diminishes behavioral and neural responses to both sweet and umami taste stimuli [28, 36]. Therefore, lack of effect of *Tas1r3* polymorphisms on taste responses to sweet amino acids and umami taste stimuli suggests that they bind to a different site than do sweeteners, responses to which are affected by the I60T polymorphism in *Tas1r3*. Taste responses to glucose polymers were not affected by natural *Tas1r*3 polymorphisms or *Tas1r3* gene knockout [116, 117], which suggests that taste of complex carbohydrates [118] is mediated by a receptor other than T1R3 (see below). Although T1R2 is a part of the sweet taste receptor and T1R1 is a part of umami/amino acid taste receptor, there is no evidence that *Tas1r2* or *Tas1r1* polymorphisms are associated with mouse strain differences in responses to sweet or umami taste stimuli.

BITTER TASTE

Bitter taste quality likely evolved as a mechanism for avoiding toxic foods. Bitter compounds evoke innate aversive behavior in many animal species. A large number of chemically diverse compounds elicit bitter taste in humans and taste aversion in nonhuman animals [119]. Toxins contained in plants and produced by micro-organisms are probably the stimuli that shaped species-specific repertoires of bitter taste receptors. Many oral medications have bitter taste, which may interfere with treatment compliance in human and veterinary medicine.

Bitter Taste Receptors

GPCRs from the T2R family function as mammalian bitter taste receptors (Fig. 1b) [120–122]. Depending on the GPCR classification system, T2Rs are described as distantly related to class A (rhodopsin-like) GPCRs [120], as belonging to a separate putative family [30–32], or as forming a distinct cluster within the frizzled/taste2 family [33].

Most vertebrate species have multiple T2R genes, and their numbers differ widely among species (Table 2). Many species have pseudogenes in addition to functional T2R genes. Symbols for genes encoding T2R proteins begin with *TAS2R* (in humans) or *Tas2r* (in other species), with the genes named taste receptor, type 2, member *n*. Besides differences in symbol letters (upper- or lowercase), human and mouse T2R genes can also be distinguished by member numbers: less than 100 for human genes (e.g., *TAS2R1-TAS2R65*), versus higher than 100 for mouse genes (e.g., *Tas2r102-Tas2r146*). Genes and proteins of other species can be distinguished by adding a lowercase letter indicating species, for example, rT2R9 for rat. In many species, T2R genes cluster in a few chromosomal locations. For example, human T2R genes map to chromosomes 5, 7, and 12, and mouse T2R genes map to chromosomes 2, 6, and 15. The T2R genes are intronless, at least in their coding region, and encode GPCR proteins that consist of ~300–330 amino acids and have a short extracellular N-terminus (Fig. 1b).

T2Rs are expressed in type II taste bud cells, and their expression does not overlap with T1Rs (with the exception of zebrafish, in which a small number of taste cells co-expresses T2Rs with T1Rs [264]). It was suggested that multiple T2Rs are co-expressed in the same taste bud cells, and possibly nearly all T2Rs are expressed in each T2R-positive cell [120, 123, 124]. However, other studies suggest that different taste bud cells may express different sets of T2Rs [122, 125]. Both possibilities find support in behavioral and neurophysiological studies, some of which suggest that different bitter compounds have identical taste quality [126–129], while others suggest that the taste system can discriminate among different bitter taste stimuli [130–132].

Most human T2Rs have been de-orphanized, mainly through the use of heterologous cell assays, and in all cases ligands were bitter-tasting compounds [133]. The number of compounds perceived by humans as bitter [119] is much larger than the number of human *TAS2R* genes, implying that each human T2R responds to more than one bitter ligand [134]. Consistent with this, several T2Rs are broadly tuned to detect stimuli of different chemical classes, while others appear to be more specific, activated by one or a few agonists [133]. It has been suggested that different T2R alleles may have different profiles of ligand specificity [99, 135–137]. Thus, the repertoire of bitter taste receptors may be not limited by the number of the *TAS2R* genes but instead may involve as many receptors as there are *TAS2R* alleles [137]. Compared with data in humans, few ligands for the T2R receptors have been experimentally confirmed for other species (reviewed in [148]). One non-human T2R that has been de-orphanized is the mouse receptor encoded by the *Tas2r105* gene, which responds to cycloheximide *in vitro* [121]. Consistent with this, *Tas2r105*-knockout mice have selective impairment in taste responses to cycloheximide but not to other bitter or nonbitter taste stimuli [123].

In addition to activating T2R receptor proteins, some bitter compounds can interact with ion channels in the cell membrane or with intracellular targets [38–40, 138–141], which thus also function as receptors of these compounds.

Between-Species Variation of Bitter Taste Receptors

Bitter taste functions to prevent consumption of toxins with food. Because animal species differ in their diets, it is reasonable to expect that different species have unique repertoires of bitter taste receptors, shaped by natural selection.

Because many plants are bitter to humans, it has been proposed that high tolerance for bitterness would be adaptive for herbivores, which was supported by observations of lower taste sensitivity to some bitter compounds in some herbivorous species compared with omnivores or carnivores [142–144]. However, recent studies have shown that this relationship is more complex. For example, some bitter compounds (salicin and protein hydrolysates) evoked stronger avoidance in herbivores than in omnivores [145, 146]. Thus, bitter taste avoidance is species and stimulus dependent, and the premise that herbivores have a generalized reduced bitter sensitivity is not accurate.

Other examples of species differences in bitter taste include phenylthiocarbamide (PTC) and phenyl-β-D-glucopyranoside, which taste bitter to humans but are not aversive to mice [123, 147]. Compared with humans, mice are more sensitive to cycloheximide and less sensitive to denatonium (A. Bachmanov, unpublished data).

Although ligands for the T2R receptors have been experimentally confirmed for only a few species (reviewed in [148]), it is likely that T2Rs function as bitter taste receptors across vertebrates. For example, fish T2Rs are involved in the taste-evoked aversive behavior [262]. Available data for a few orthologous pairs of T2Rs suggest that receptor sequence similarity is predictive of the receptor ligand specificity. Rat and mouse *Tas2r105* orthologs respond to cycloheximide [121, 149]. Orthologous human *TAS2R4* and mouse *Tas2r108* respond to denatonium and 6-n-propyl-2-thiouracil (PROP) [121]. Sensitive alleles of human *TAS2R38* and chimpanzee *Tas2r38* orthologs respond to PTC [150, 151]. On the other hand, non-orthologous T2Rs in different species may be activated by the same agonists. For example, some fish T2Rs are activated by denatonium, but they are not orthologs of the mammalian denatonium receptors [262].

As mentioned above, numbers of T2R genes in vertebrate species differ widely (Table 2). Many species have T2R pseudogenes in addition to functional T2R genes, although birds and fishes seem to lack or have small numbers of pseudogenes compared with mammals, reptiles, and amphibians. The largest number of functional or putatively functional T2Rs was predicted in the western clawed frog (n=52), while the bottlenose dolphin appears to completely lack functional T2Rs. Numbers of functional or putatively functional T2Rs also differ widely within each characterized class of animals: from 0 to 37 in mammals, from 3 to 19 in birds, and from 0 to 6 in fish.

Analyses of relatedness of the T2R genes in different species suggest a complex evolution of this gene family. Local and inter-chromosomal duplications, deletions, pseudogenization,

and positive selection drove expansions and contractions of T2R repertoires in different lineages [64, 152–155]. However, little is known about how this variation in T2R repertoires affects species differences in bitter taste.

Within-Species Variation of Bitter Taste Receptors

Humans—Human *TAS2R* genes have substantial diversity of coding sequence, including segregating pseudogenes [136, 137, 156, 157]. This suggests that *TAS2R* polymorphisms may be responsible for individual differences in bitter taste (reviewed in [98–100, 158]). However, this relationship has been demonstrated for only a few genes.

TAS2R38 was identified in a positional cloning study [159] as a gene identical to a human PTC bitter taste sensitivity locus on chromosome 7q [160]. Allelic variants of *TAS2R38* are associated with human perception of PTC and PROP bitterness [150, 159, 161–163]. PTC and PROP responses of cells heterologously expressing different alleles of *TAS2R38* correlate with psychophysical responses of individuals carrying these alleles [150]. While wild-type mice do not show strong aversion of PTC in brief-access tests [147], mice with a taster allele of human *TAS2R38* transgenically expressed in bitter-sensing cells under the control of a mouse *Tas2r* promoter show strong aversion to PTC [123].

Sensitive alleles of T2R38 respond to PTC, PROP, and related compounds that contain a thiourea (N-C=S) moiety. Some plants consumed by humans contain glucosinolates, which also contain the thiourea moiety, and *TAS2R38* genotype can affect perception of bitterness of these plants, such as broccoli, turnips, and horseradish [164].

Although a PTC “nontaster” allele of *TAS2R38* is expressed in taste buds, it does not respond to taste stimuli *in vitro* [150]. Because taster and nontaster alleles of *TAS2R38* are maintained by balanced selection [165], it has been suggested that the “nontaster” allele may serve as a functional receptor for toxic bitter substances other than PTC that have not yet been identified [99, 135, 136, 165].

Signs of positive selection were also found for *TAS2R16* encoding a receptor for β-glucopyranosides. Its ancestral allele associated with lower sensitivity to β-glucopyranosides is under positive selection only in central Africa, while the evolutionarily derived allele associated with an increased sensitivity is under positive selection in the rest of the world. It is suggested that the global pattern of allelic variation of the *TAS2R16* gene depends on selective pressures of protection against malaria in Africa and protection against toxins in malaria-free zones [166].

T2R31 is a receptor for bitterness of artificial sweeteners, saccharin, and acesulfame K. Polymorphisms in the *TAS2R31* gene were associated with perception of bitterness of these sweeteners in both human subjects and *in vitro* assays [167]. Taste perception of quinine was associated with a cluster of T2R and salivary proline-rich protein genes on chromosome 12, but tight linkage among these genes precluded the identification of a single causal genetic variant [168].

Chimpanzee—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* [151]. However, variation in PTC taste sensitivity in chimpanzees depends on *Tas2r38* alleles different from those in humans. While taster and nontaster alleles of the human *TAS2R38* gene are defined by missense SNPs [159, 165], the PTC-insensitive allele of chimpanzee *Tas2r38* encodes a truncated receptor variant [151]. Thus, nontaster *Tas2r38* alleles have been independently derived in humans and chimpanzees [151].

Mice—Mouse strains differ in taste responses to bitter taste stimuli. Several genetic loci are responsible for variation in aversion to bitter-tasting quinine (*Qui*), cycloheximide (*Cyx*), copper glycinate (*Glb*), and the acetylated sugars sucrose octaacetate and raffinose undecaacetate (*Soa/Rua*), all of which map to the mouse chromosome 6, in a T2R gene cluster region (reviewed in [5, 7]). There is also considerable strain variation in sequences of the mouse T2R genes [121, 147, 169], suggesting that the genetic variation in bitter taste is due to polymorphisms of the T2R genes, as predicted by Lush [109]. However, this relationship has been demonstrated for only the *Tas2r105* gene corresponding to the *Cyx* locus [121, 123, 147], although with some inconsistencies (see [3, 170]).

SALTY TASTE

Hedonic responses (attraction or avoidance) to salty taste depend on species, genotype, stimulus concentration, and physiological state of individuals. At lower concentrations, salty taste is often attractive, but at high concentrations it is typically aversive. Sodium balance of the body strongly influences hedonics of salty taste, with sodium depletion known to induce salt appetite in many species [171, 172].

A prototypical salty taste stimulus is sodium chloride (NaCl). LiCl also has predominantly salty taste. Many other sodium and nonsodium salts taste salty, but their saltiness is usually accompanied by additional taste quality components, most frequently described as bitterness [173].

Salty Taste Receptors

Earlier studies suggested that there are at least two transduction pathways for salty taste. This hypothesis was based on findings that amiloride, a potassium-sparing diuretic, partially suppresses taste responses to sodium and lithium salts [174–176]. Because amiloride blocks the epithelial sodium channel (ENaC), the portion of taste responses suppressed by amiloride (amiloride sensitive) is proposed to be mediated by ENaC. The portion of taste response that is not inhibited by amiloride is considered amiloride insensitive. Amiloride-sensitive and -insensitive transduction pathways of salty taste have distinct properties. The amiloride-sensitive mechanism is cation (Na^+ and Li^+) selective; the amiloride-insensitive mechanism is cation nonselective and can be activated by both sodium and nonsodium salts, such as KCl and NH_4Cl.

ENaC is a member of the degenerin/ENaC superfamily of ion channels. The ENaC channel is a heteromer consisting of several different subunits: α, β, γ, and/or δ. Each ENaC subunit

has two transmembrane domains and is encoded by a separate gene (Fig. 1c). Humans have four ENaC channel subunits, α, β, γ, and δ, encoded by the non-voltage-gated sodium channel 1 genes *SCNN1A*, *SCNN1B*, *SCNN1G*, and *SCNN1D*, respectively. Mice and rats lack the ENaCδ subunit [177] and therefore have only three ENaC subunits encoded by *Scnn1a*, *Scnn1b*, and *Scnn1g*. The genes for ENaC β and γ subunits are closely linked and located in humans on chromosome 16 and in mice in a region of conserved synteny on chromosome 7. The ENaCα gene is on human chromosome 12, and in the mouse it is on chromosome 6. Human ENaCδ is on chromosome 1, and in the mouse it is a pseudogene located on chromosome 4 [178].

ENaC is involved in transepithelial ion transport in many tissues (e.g., kidney, lung). Correspondingly, ENaC subunits are expressed in many epithelial tissues, including taste and nontaste lingual epithelial cells [179–182]. Based on suppression of taste responses to sodium by amiloride in some species, and based on ENaC expression in taste tissues, ENaC was proposed as a candidate component of salty taste transduction system (reviewed in [183–185]). Recent work with mice genetically engineered to lack ENaC in taste cells [186, 187] has conclusively established the importance of this channel in mediating sodium taste in mice. However, it is still not clear what other components are involved in the amiloride-sensitive salt taste transduction pathway or how they interact with ENaC.

Mechanisms for transduction of amiloride-insensitive cation-nonselective salt taste are even less understood. Earlier studies suggested that amiloride-insensitive salty taste can be explained by diffusion of sodium through tight junctions that are impermeable to amiloride; as a result, Na^+ would stimulate taste bud cells through basolateral ENaC channels, which are not accessible to, and therefore are not blocked by, amiloride [139, 188, 189]. However, this paracellular pathway hypothesis is not consistent with existence of taste bud cells, in which responses to apical application of NaCl are not inhibited by amiloride [190]. The Cl^- anion was also proposed to be responsible for amiloride-insensitive NaCl taste [191], but experiments with known mechanisms of transmembrane transport of Cl^- did not confirm their involvement in salty taste [192, 193]. A recent study showed that concentrated solutions of sodium and nonsodium salts activate two populations of taste bud cells: type II cells expressing T2R receptors, which are also activated by bitter compounds, and type III cells, some of which are also activated by acids. Activation of these cells by salts triggers aversive behavioral response [194]. However, the biological molecules mediating amiloride-insensitive salt taste response have not yet been conclusively identified, although candidates have been proposed.

One candidate is TRPV1 (transient receptor potential cation channel, subfamily V, member 1; formerly named vanilloid receptor subtype 1, or capsaicin receptor). TRPV1 is a transducer of painful thermal stimuli and is also activated by capsaicin, a pungent ingredient in “hot” chili peppers [195]. Based on taste nerve recording experiments using TRPV1 agonists and antagonists and *Trpv1*-knockout mice, a TRPV1 variant was proposed to function as an amiloride-insensitive salt taste receptor in rodents [196]. However, *Trpv1*-knockout mice do not have deficiencies in behavioral taste responses to salt [197 198]. Moreover, recent studies did not confirm initial findings of effects of TRPV1 antagonists and *Trpv1* gene knockout on taste nerve responses [199, 200]. In addition, data on

expression of TRPV1 in the lingual tissue are also inconsistent with its role in salt taste reception. Some immunohistochemical studies detected its expression in rat trigeminal afferent neurons innervating the oral cavity but not in taste bud cells [201, 202]. In another study, TRPV1 immunoreactivity has been detected in rat taste bud cells expressing T1R and T2R receptors [203]. If TRPV1 functions as a salt taste receptor, then co-expression of TRPV1 with T1Rs would suggest that salts should activate T1R-expressing cells, which contradicts some findings [194]. It is likely that TRPV1 contributes to oral chemosensory responses to salts through its expression in trigeminal (somatosensory) nerve endings [200, 204], but not in taste bud cells.

A second candidate for amiloride-insensitive salt taste receptor is TRPML3 (MCOLN3, mucolipin 3), which, like TRPV1, belongs to the transient receptor potential (TRP) family of cation channels [205]. However, mouse taste receptor cells do not appear to express physiologically relevant levels of TRPML3 [206].

Between-Species Variation of Salty Taste Receptors

Animal species differ in their avidity for salt. For example, licking crystallized salt is common among wild animals, particularly herbivores, whose food contains little sodium. On the other hand, meat, the diet of strict carnivores, has sufficient sodium to satisfy their bodily needs [172, 173]. Species differences in need-induced salt appetite may have central rather than peripheral origin. Nevertheless, species differences in peripheral taste mechanisms may also exist.

The best-known example of possible species differences in salty taste reception is sensitivity to amiloride. Neural and/or behavioral taste responses to NaCl are attenuated by amiloride in the mouse, rat, gerbil, hamster, dog, rhesus monkey, and frog [184]. However, amiloride generally does not change perception of saltiness in humans but reduces total intensity and sourness of NaCl and LiCl [184 207]. These species differences may be attributed to presence of the ENaCδ subunit in humans but not rodents. Because ENaCδ is expressed in human taste bud cells [208, 209], it was proposed that the substitution of ENaCα with ENaCδ in the human salty taste receptor deems it less amiloride sensitive [210], consistent with known substantially reduced amiloride sensitivity of δβγ ENaC channel compared with αβγ ENaC [211]. It was proposed that the amiloride-sensitive gustatory mechanisms may be of minor importance for human taste [184]. However, this does not mean that ENaC is not involved in human salty taste, because differences in subunit composition of the ENaC channel may be responsible for species differences in amiloride sensitivity of salty taste.

If ENaCδ explains reduced amiloride sensitivity of salty taste in humans, other species with an intact ENaCδ gene should also have diminished amiloride sensitivity of salty taste. ENaCδ is annotated in genomes of several species. In addition to several primate species, it is present in the dog, cat, cow, sheep, horse, guinea pig, Tasmanian devil, and chicken ([212] and http://www.ncbi.nlm.nih.gov). (The gene annotated as *Scnn1d* in the African clawed frog, *Xenopus laevis*, encodes the ENaCε subunit [212]). Amiloride-sensitive NaCl taste responses have been described in dogs and some primates, species with intact ENaCδ [184, 213, 214]. This brings into question whether presence or absence of ENaCδ can explain amiloride sensitivity or insensitivity across all animal species. However, it is not

known whether ENaCδ is expressed in taste bud cells of these animals, as it is in humans. Furthermore, amiloride sensitivity in these animals was characterized using taste nerve recordings, but such data are not available for humans. In mice, amiloride sensitivity to NaCl does not always correlate well between behavioral and neural responses (e.g., [215]). Similarly, the contribution of ENaCδ may be different for amiloride sensitivity of behavioral and neural responses to NaCl.

It is interesting that salt taste responses in *Drosophila* involve degenerin/ENaC channels PPK11 and PPK19 [216], suggesting that salt-sensing mechanisms by degenerin/ENaC channels may have evolved in a common ancestor of vertebrate and invertebrate animals.

Within-Species Variation of Salty Taste Receptors

Previous studies reported individual variation in human salty taste perception and differences among mouse and rat strains in salt preferences and amiloride sensitivity of chorda tympani responses to NaCl (reviewed in [5–7]). Inbred mouse strains also differ in NaCl taste thresholds [217]. Polymorphisms of ENaC subunit genes have been associated with amiloride sensitivity of NaCl taste responses in mice [218] and humans [219].

SOUR TASTE

Sour taste is evoked by acids. Protons are the critical stimulus, although sourness can be affected by the anion. For example, sourness of organic acids is stronger than sourness of inorganic acids at the same pH. Acids can stimulate not only gustatory but also oral somatosensory chemoreceptors. However, gustatory and somato-sensory responses to acids can be distinguished based on acid concentrations. Typically, responses to dilute acid solutions are predominantly gustatory, and a somatosensory component requires higher acid concentrations (discussed in [220]).

Sour Taste Receptors

A sour taste receptor is presumably an ion channel. Several candidate sour (acid) taste receptors have been proposed, but none has been definitely proven (reviewed in [3]). Recent studies suggested that ion channels encoded by the genes *Pkd1l3* and *Pkd2l1* (polycystic kidney disease-1- and -2-like) function as sour taste receptors [221–223]. However, targeted mutations in these genes have no or only modest effect on taste responses to acids [220, 224].

Between-Species Variation in Sour Taste

Animals of many species detect, and typically avoid, sour taste. We are not aware of any published data on species differences in sour taste. It is possible that all species have similar needs for orosensory detection of acids, and thus sour taste may be conserved across species.

Within-Species Variation in Sour Taste

Genetics likely contributes to within-species differences in sour taste: heritable differences in sour taste were reported in human twins [225] and among inbred mouse strains [226]. These genetic studies may assist with identification of the still elusive sour taste receptor

through the positional cloning approach, which facilitated identification of T1R and T2R receptors (e.g., [159, 178]).

TASTE RECEPTORS FOR NONCANONICAL AND COMPLEX TASTE STIMULI

Water

Water consumption is crucial for animals' survival and is regulated by thirst, a specialized water appetite [171]. Therefore, animals must be able to detect water or hypo-osmotic fluids through oral chemosensation. Consistent with this, water can evoke taste responses (reviewed in [139, 227]). Aquaporins are expressed in taste receptor cells and were proposed as sensors for hypo-osmotic stimuli [227, 228].

Taste perception of water by humans depends on preceding adaptation of the oral cavity to different taste solutions (and probably to saliva) [229–232]. 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" [233]. This adaptation-dependent perception of water taste is mediated by the T1R2+3 sweet taste receptor: washing out a sweet taste inhibitor with water shifts the receptor from an inactive to an active state, which initiates transduction events evoking perception of sweetness [234].

Ethanol

Ethanol evokes sweet and bitter taste (reviewed in [235]). Consistent with this, alcohol consumption is associated with allelic variants of the *Tas1r3* sweet taste receptor gene in mice and *TAS2R* bitter taste receptor genes in humans. A more sensitive *Tas1r3* allele makes the pleasant sweet taste component of ethanol stronger and facilitates consumption of ethanol by mice [236]. More sensitive alleles of the *TAS2R* genes make the unpleasant bitter taste component of ethanol stronger and suppress alcohol consumption in humans [163, 237].

Kokumi and Calcium

Kokumi is derived from the Japanese word *koku* (こく; "body") in the same way as *umami* is derived from the word *umai*. Kokumi describes oral sensations of continuity, mouthfulness and thickness, and enhancement of basic taste sensations. Examples of kokumi substances are glutathione and some other γ-glutamyl peptides contained in foodstuffs [238, 239]. Kokumi compounds activate the extracellular calcium-sensing receptor (CaSR) [240] that is expressed in taste bud cells [241]. Activation of CaSR-expressing taste bud cells [242] by kokumi substances suggests that kokumi can be categorized as a taste sensation, although the definition of kokumi as a taste quality remains debatable.

Calcium salts stimulate taste [243], which can be mediated by the T1R3 receptor [244, 245] in addition to the CaSR.

Fat

The fatty acid transporter CD36 and GPCRs GPR40 and GPR120 are expressed in taste bud cells and have been proposed to be involved in oral detection of fatty acids [246–254]. Polymorphisms of the human *CD36* gene have been associated with oral fat perception [255, 256].

Complex Carbohydrates

Rats and some other species perceive taste of polysaccharides as qualitatively distinct from taste of sugars [118]. However, a molecular mechanism for perception of complex carbohydrates is unknown.

CONCLUSION

This review demonstrates how gene structure and variation influence expression and function of taste receptors, which affects how the taste system functions. The two main types of gene variation, orthologous genes in different species and alleles within species, account for variations in behaviors toward tastes between and within species. Although taste receptors for sweet and umami (T1R), bitter (T2R), and salty (ENaC) are known, we know little about their across-species variations, and sour taste and ENaC-independent salt taste are still poorly understood. Other, noncanonical taste receptors have been proposed, including those that detect water, fat, and complex carbohydrates, though much research remains to confirm them and uncover their mechanisms. These and other as yet discovered taste receptors can be targets for screening novel taste compounds. Thus, further research in these areas holds the promise of improved nutrition, health, and well-being.

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ABBREVIATIONS

CaSR	Calcium-sensing receptor
ENaC	Epithelial sodium channel
GPCR	G protein-coupled receptor
mGluR	Metabotropic glutamate receptor
MSG	Monosodium glutamate
PROP	6-n-propyl-2-thiouracil
PTC	Phenylthiocarbamide
SNP	Single-nucleotide polymorphism
T1R	Taste receptor, type 1
T2R	Taste receptor, type 2

LITERATURE CITED

1. Yarmolinsky DA, Zuker CS, Ryba NJ. Common sense about taste: from mammals to insects. Cell. 2009; 139:234–44. [PubMed: 19837029]
2. Montell C. A taste of the Drosophila gustatory receptors. Curr Opin Neurobiol. 2009; 19:345–53. [PubMed: 19660932]
3. Bachmanov AA, Beauchamp GK. Taste receptor genes. Annu Rev Nutr. 2007; 27:389–414. [PubMed: 17444812]
4. Bachmanov AA, Bosak NP, Floriano WB, et al. Genetics of sweet taste preferences. Flavour Fragr J. 2011; 26:286–294. [PubMed: 21743773]
5. Boughter, JD.; Bachmanov, AA. Genetics and evolution of taste. In: Firestein, S.; Beauchamp, GK., editors. Olfaction and Taste. Elsevier/Academic Press; San Diego: 2008. p. 371-390.
6. Bachmanov, AA.; Boughter, JD. eLS 2012. John Wiley & Sons, Ltd; Chichester: 2012. Genetics of Taste Perception. http://www.els.net/
7. Boughter JD Jr, Bachmanov AA. Behavioral genetics and taste. BMC Neurosci. 2007; 8(Suppl 3):S3. [PubMed: 17903279]
8. Bachmanov AA. Genetic approach to characterize interaction of sweeteners with sweet taste receptors *in vivo*. Chem Senses. 2005; 30(Suppl 1):i82–i83. [PubMed: 15738207]
9. Slack JP, Brockhoff A, Batram C, et al. Modulation of bitter taste perception by a small molecule hTAS2R antagonist. Curr Biol. 2010; 20:1104–9. [PubMed: 20537538]
10. Greene TA, Alarcon S, Thomas A, et al. Probenecid inhibits the human bitter taste receptor TAS2R16 and suppresses bitter perception of salicin. PLoS One. 2011; 6:e20123. [PubMed: 21629661]
11. Servant G, Tachdjian C, Tang XQ, et al. Positive allosteric modulators of the human sweet taste receptor enhance sweet taste. Proc Natl Acad Sci USA. 2010; 107:4746–51. [PubMed: 20173092]
12. Margolskee RF, Dyer J, Kokrashvili Z, et al. T1R3 and gustducin in gut sense sugars to regulate expression of Na+-glucose cotransporter 1. Proc Natl Acad Sci USA. 2007; 104:15075–80. [PubMed: 17724332]
13. Lee RJ, Xiong G, Kofonow JM, et al. T2R38 taste receptor polymorphisms underlie susceptibility to upper respiratory infection. J Clin Invest. 2012; 122:4145–59. [PubMed: 23041624]
14. Janssen S, Depoortere I. Nutrient sensing in the gut: new roads to therapeutics? Trends Endocrinol Metab. 2013; 24:92–100. [PubMed: 23266105]
15. Behrens M, Meyerhof W. Gustatory and extragustatory functions of mammalian taste receptors. Physiol Behav. 2011; 105:4–13. [PubMed: 21324331]
16. McCaughey SA. The taste of sugars. Neurosci Biobehav Rev. 2008; 32:1024–43. [PubMed: 18499254]
17. Steiner JE, Glaser D, Hawilo ME, Berridge KC. Comparative expression of hedonic impact: affective reactions to taste by human infants and other primates. Neurosci Biobehav Rev. 2001; 25:53–74. [PubMed: 11166078]
18. Berridge KC. Measuring hedonic impact in animals and infants: microstructure of affective taste reactivity patterns. Neurosci Biobehav Rev. 2000; 24:173–98. [PubMed: 10714382]
19. DuBois, GE. New insights on the coding of the sweet taste message in chemical structure. In: Salvadori, G., editor. Firmenich Jubilee Symposium 1895–1995. Allured Publishing Corp; Carol Stream, IL, USA: Geneva, Switzerland: 1995. p. 32-95.
20. Schiffman SS, Gatlin CA. Sweeteners: State of knowledge review. Neurosci Biobehav Rev. 1993; 17:313–345. [PubMed: 8272285]
21. Ikeda K. New seasonings. Chem Senses. 2002; 27:847–9. [PubMed: 12438213]
22. Bachmanov AA. Umami: Fifth taste? Flavor enhancer? Perfumer and Flavorist. 2010; 35:52–57.
23. Ninomiya Y, Funakoshi M. Behavioural discrimination between glutamate and the four basic taste substances in mice. Comp Biochem Physiol. 1989; 92:365–370.
24. Ninomiya Y, Funakoshi M. Peripheral neural basis for behavioural discrimination between glutamate and the four basic taste substances in mice. Comp Biochem Physiol. 1989; 92:371–376.

25. Murata Y, Beauchamp GK, Bachmanov AA. Taste perception of monosodium glutamate and inosine monophosphate by 129P3/J and C57BL/6ByJ mice. Physiol Behav. 2009; 98:481–8. [PubMed: 19666040]
26. Nelson G, Hoon MA, Chandrashekar J, et al. Mammalian sweet taste receptors. Cell. 2001; 106:381–90. [PubMed: 11509186]
27. Li X, Staszewski L, Xu H, et al. Human receptors for sweet and umami taste. Proc Natl Acad Sci USA. 2002; 99:4692–6. [PubMed: 11917125]
28. Zhao GQ, Zhang Y, Hoon MA, et al. The receptors for mammalian sweet and umami taste. Cell. 2003; 115:255–66. [PubMed: 14636554]
29. Nelson G, Chandrashekar J, Hoon MA, et al. An amino-acid taste receptor. Nature. 2002; 416:199–202. [PubMed: 11894099]
30. Kolakowski LF Jr. GCRDb: a G-protein-coupled receptor database. Receptors Channels. 1994; 2:1–7. [PubMed: 8081729]
31. Attwood TK, Findlay JB. Fingerprinting G-protein-coupled receptors. Protein Eng. 1994; 7:195–203. [PubMed: 8170923]
32. GPCRDB. Information system for G protein-coupled receptors (GPCRs). http://www.gpcr.org/7tm/
33. Fredriksson R, Lagerstrom MC, Lundin LG, Schioth HB. The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogon groups, and fingerprints. Mol Pharmacol. 2003; 63:1256–72. [PubMed: 12761335]
34. Max M, Shanker YG, Huang L, et al. Tas1r3, encoding a new candidate taste receptor, is allelic to the sweet responsiveness locus *Sac*. Nat Genet. 2001; 28:58–63. [PubMed: 11326277]
35. Montmayeur JP, Liberles SD, Matsunami H, Buck LB. A candidate taste receptor gene near a sweet taste locus. Nat Neurosci. 2001; 4:492–8. [PubMed: 11319557]
36. Damak S, Rong M, Yasumatsu K, et al. Detection of sweet and umami taste in the absence of taste receptor T1r3. Science. 2003; 301:850–3. [PubMed: 12869700]
37. Yee KK, Sukumaran SK, Kotha R, Gilbertson TA, Margolskee RF. Glucose transporters and ATP-gated K+ (KATP) metabolic sensors are present in type 1 taste receptor 3 (T1r3)-expressing taste cells. Proc Natl Acad Sci USA. 2011; 108:5431–5436. [PubMed: 21383163]
38. Naim, M.; Nir, S.; Spielman, AI., et al. Hypothesis of receptor-dependent and receptor-independent mechanisms for bitter and sweet taste transduction: Implications for slow taste onset and lingering aftertaste. In: Given, P.; Parades, D., editors. Chemistry of Taste: Mechanisms, Behaviors, and Mimics. American Chemical Society; Washington, DC: 2002. p. 2-17.ACS symposium series; 825
39. Peri I, Mamrud-Brains H, Rodin S, et al. Rapid entry of bitter and sweet tastants into liposomes and taste cells: implications for signal transduction. Am J Physiol Cell Physiol. 2000; 278:C17–25. [PubMed: 10644507]
40. Zubare-Samuelov M, Shaul ME, Peri I, et al. Inhibition of signal termination-related kinases by membrane-permeant bitter and sweet tastants: potential role in taste signal termination. Am J Physiol Cell Physiol. 2005; 289:C483–92. [PubMed: 15829560]
41. Chaudhari N, Yang H, Lamp C, et al. The taste of monosodium glutamate: membrane receptors in taste buds. J Neurosci. 1996; 16:3817–3826. [PubMed: 8656276]
42. Chaudhari N, Roper SD. Molecular and physiological evidence for glutamate (umami) taste transduction via a G protein-coupled receptor. Ann N Y Acad Sci. 1998; 855:398–406. [PubMed: 9929632]
43. Chaudhari N, Landin AM, Roper SD. A metabotropic glutamate receptor variant functions as a taste receptor. Nat Neurosci. 2000; 3:113–9. [PubMed: 10649565]
44. San Gabriel A, Uneyama H, Yoshie S, Torii K. Cloning and characterization of a novel mGluR1 variant from vallate papillae that functions as a receptor for L-glutamate stimuli. Chem Senses. 2005; 30(Suppl 1):i25–i26. [PubMed: 15738140]
45. Brand JG. Receptor and transduction processes for umami taste. J Nutr. 2000; 130:942S–5S. [PubMed: 10736357]
46. Hayashi Y, Zviman MM, Brand JG, Teeter JH, Restrepo D. Measurement of membrane potential and $[Ca^{2+}]i$ in cell ensembles: application to the study of glutamate taste in mice. Biophys J. 1996; 71:1057–1070. [PubMed: 8842242]

47. Toyono T, Seta Y, Kataoka S, et al. Expression of metabotropic glutamate receptor group I in rat gustatory papillae. Cell Tissue Res. 2003; 313:29–35. [PubMed: 12898387]
48. Toyono T, Seta Y, Kataoka S, et al. Expression of the metabotropic glutamate receptor, mGluR4a, in the taste hairs of taste buds in rat gustatory papillae. Arch Histol Cytol. 2002; 65:91–6. [PubMed: 12002614]
49. Lin W, Ogura T, Kinnamon SC. Responses to di-sodium guanosine 5′-monophosphate and monosodium L-glutamate in taste receptor cells of rat fungiform papillae. J Neurophysiol. 2003; 89:1434–9. [PubMed: 12626621]
50. Grosvenor W, Kaulin Y, Spielman AI, et al. Biochemical enrichment and biophysical characterization of a taste receptor for L-arginine from the catfish, Ictalurus puntatus. BMC Neurosci. 2004; 5:25. [PubMed: 15282034]
51. Grosvenor W, Feigin AM, Spielman AI, et al. The arginine taste receptor. Physiology, biochemistry, and immunohistochemistry. Ann N Y Acad Sci. 1998; 855:134–42. [PubMed: 9929594]
52. Kumazawa T, Brand JG, Teeter JH. Amino acid-activated channels in the catfish taste system. Biophys J. 1998; 75:2757–66. [PubMed: 9826598]
53. Finger TE, Bryant BP, Kalinoski DL, et al. Differential localization of putative amino acid receptors in taste buds of the channel catfish, Ictalurus punctatus. J Comp Neurol. 1996; 373:129–38. [PubMed: 8876468]
54. Beauchamp GK, Maller O, Rogers JG. Flavor preferences in cats (Felis catus and Panthera sp.) J Comp Physiol Psychol. 1977; 91:1118–1127.
55. Bartoshuk LM, Jacobs HL, Nichols TL, Hoff LA, Ryckman JJ. Taste rejection of nonnutritive sweeteners in cats. J Comp Physiol Psychol. 1975; 89:971–5. [PubMed: 1184803]
56. Halpern BP. Gustatory nerve responses in the chicken. Am J Physiol. 1962; 203:541–4. [PubMed: 13903995]
57. Ganchrow JR, Steiner JE, Bartana A. Behavioral reactions to gustatory stimuli in young chicks (*Gallus gallus domesticus*). Dev Psychobiol. 1990; 23:103–17. [PubMed: 2365134]
58. Kare, MR. Comparative aspects of the sense of taste. In: Kare, MR.; Halpern, BP., editors. Physiological and Behavioral Aspects of Taste. The University of Chicago Press; Chicago: 1961. p. 6-15.
59. Li X, Glaser D, Li W, et al. Analyses of sweet receptor gene (Tas1r2) and preference for sweet stimuli in species of Carnivora. J Hered. 2009; 100(Suppl 1):S90–100. [PubMed: 19366814]
60. Glaser D, Tinti JM, Nofre C. Evolution of the sweetness receptor in primates. I. Why does alitame taste sweet in all Prosimians and Simians, and aspartame only in Old World Simians? Chem Senses. 1995; 20:573–584. [PubMed: 8564432]
61. Bachmanov AA, Tordoff MG, Beauchamp GK. Sweetener preference of C57BL/6ByJ and 129P3/J mice. Chem Senses. 2001; 26:905–13. [PubMed: 11555485]
62. Roura E, Humphre B, Klasingc K, Swartd M. Is the pig a good umami sensing model for humans? A comparative taste receptor study. Flavour Fragr J. 2011; 26:282–285.
63. Ishimaru Y, Okada S, Naito H, et al. Two families of candidate taste receptors in fishes. Mech Dev. 2005; 122:1310–21. [PubMed: 16274966]
64. Shi P, Zhang J. Contrasting modes of evolution between vertebrate sweet/umami receptor genes and bitter receptor genes. Mol Biol Evol. 2006; 23:292–300. [PubMed: 16207936]
65. Zhao H, Yang JR, Xu H, Zhang J. Pseudogenization of the umami taste receptor gene Tas1r1 in the giant panda coincided with its dietary switch to bamboo. Mol Biol Evol. 2010; 27:2669–73. [PubMed: 20573776]
66. Li R, Fan W, Tian G, et al. The sequence and de novo assembly of the giant panda genome. Nature. 2010; 463:311–7. [PubMed: 20010809]
67. Sato JJ, Wolsan M. Loss or major reduction of umami taste sensation in pinnipeds. Naturwissenschaften. 2012; 99:655–9. [PubMed: 22777285]
68. Zhao H, Xu D, Zhang S, Zhang J. Genomic and genetic evidence for the loss of umami taste in bats. Genome Biol Evol. 2011; 4:73–9. [PubMed: 22117084]

69. Lagerstrom MC, Hellstrom AR, Gloriam DE, et al. The G protein-coupled receptor subset of the chicken genome. PLoS Comput Biol. 2006; 2:e54. [PubMed: 16741557]
70. Zhao H, Zhou Y, Pinto CM, et al. Evolution of the sweet taste receptor gene Tas1r2 in bats. Mol Biol Evol. 2010; 27:2642–50. [PubMed: 20558596]
71. Daly K, Al-Rammahi M, Arora DK, et al. Expression of sweet receptor components in equine small intestine: relevance to intestinal glucose transport. Am J Physiol Regul Integr Comp Physiol. 2012; 303:R199–208. [PubMed: 22552794]
72. Li X, Li W, Wang H, et al. Pseudogenization of a sweet-receptor gene accounts for cats' indifference toward sugar. PLoS Genet. 2005; 1:27–35. [PubMed: 16103917]
73. Jiang P, Josue J, Li X, et al. Major taste loss in carnivorous mammals. Proc Natl Acad Sci USA. 2012; 109:4956–61. [PubMed: 22411809]
74. Grace J, Russek M. The influence of previous experience on the taste behavior of dogs toward sucrose and saccharin. Physiol Behav. 1969; 4:553–558.
75. Ferrell F. Preference for sugars and nonnutritive sweeteners in young beagles. Neurosci Biobehav Rev. 1984; 8:199–203. [PubMed: 6205334]
76. Martinez del Rio C, Stevens BR, Daneke DE, Andreadis PT. Physiological correlates of preference and aversion for sugars in three species of birds. Physiol Zool. 1988; 61:222–229.
77. Matson KD, Millam JR, Klasing KC. Thresholds for sweet, salt, and sour taste stimuli in cockatiels (*Nymphicus hollandicus*). Zoo Biol. 2001; 20:1–13. [PubMed: 11319776]
78. Stiles FG. Taste preferences, color preferences, and flower choice in humminbirds. The Condor. 1976; 78:10–26.
79. Thompson JD, Elias DJ, Shumake SA, Gaddis SE. Taste preferences of the common vampire bat (*Desmodus rotundus*). J Chem Ecol. 1982; 8:715–721. [PubMed: 24415119]
80. Danilova V, Hellekant G, Tinti JM, Nofre C. Gustatory responses of the hamster *Mesocricetus auratus* to various compounds considered sweet by humans. J Neurophysiol. 1998; 80:2102–2112. [PubMed: 9772264]
81. Bachmanov AA, Tordoff MG, Beauchamp GK. Sweetener preference of C57BL/6ByJ and 129P3/J mice. Chem Senses. 2001; 26:905–913. [PubMed: 11555485]
82. Inoue M, McCaughey SA, Bachmanov AA, Beauchamp GK. Whole-nerve chorda tympani responses to sweeteners in C57BL/6ByJ and 129P3/J mice. Chem Senses. 2001; 26:915–923. [PubMed: 11555486]
83. Winnig M, Bufe B, Meyerhof W. Valine 738 and lysine 735 in the fifth transmembrane domain of rTas1r3 mediate insensitivity towards lactisole of the rat sweet taste receptor. BMC Neurosci. 2005; 6:22. [PubMed: 15817126]
84. Jiang P, Ji Q, Liu Z, et al. The cysteine-rich region of T1R3 determines responses to intensely sweet proteins. J Biol Chem. 2004; 279:45068–75. [PubMed: 15299024]
85. Xu H, Staszewski L, Tang H, et al. Different functional roles of T1R subunits in the heteromeric taste receptors. Proc Natl Acad Sci USA. 2004; 101:14258–63. [PubMed: 15353592]
86. Jiang P, Cui M, Ji Q, et al. Molecular mechanisms of sweet receptor function. Chem Senses. 2005; 30(Suppl 1):i17–i18. [PubMed: 15738096]
87. Zhang Y, Hoon MA, Chandrashekar J, et al. Coding of sweet, bitter, and umami tastes. Different receptor cells sharing similar signaling pathways. Cell. 2003; 112:293–301. [PubMed: 12581520]
88. Jiang P, Cui M, Zhao B, et al. Identification of the cyclamate interaction site within the transmembrane domain of the human sweet taste receptor subunit T1R3. J Biol Chem. 2005; 280:34296–305. [PubMed: 16076846]
89. Jiang P, Cui M, Zhao B, et al. Lactisole interacts with the transmembrane domains of human T1R3 to inhibit sweet taste. J Biol Chem. 2005; 280:15238–46. [PubMed: 15668251]
90. Li X, Bachmanov AA, Maehashi K, et al. Sweet Taste Receptor Gene Variation and Aspartame Taste in Primates and Other Species. Chem Senses. 2011; 36:453–475. [PubMed: 21414996]
91. Liu B, Ha M, Meng XY, et al. Molecular Mechanism of Species-Dependent Sweet Taste toward Artificial Sweeteners. J Neurosci. 2011; 31:11070–6. [PubMed: 21795555]
92. Kim UK, Wooding S, Riaz N, Jorde LB, Drayna D. Variation in the human TAS1R taste receptor genes. Chem Senses. 2006; 31:599–611. [PubMed: 16801379]

93. Lu K, McDaniel AH, Tordoff MG, et al. No relationship between sequence variation in protein coding regions of the Tas1r3 gene and saccharin preference in rats. Chem Senses. 2005; 30:231–40. [PubMed: 15741599]
94. Reed DR, Li S, Li X, et al. Polymorphisms in the taste receptor gene (*Tas1r3*) region are associated with saccharin preference in 30 mouse strains. J Neurosci. 2004; 24:938–46. [PubMed: 14749438]
95. Reed DR, McDaniel AH. The human sweet tooth. BMC Oral Health. 2006; 6(Suppl 1):S17. [PubMed: 16934118]
96. Reed, DR.; Li, X.; Bachmanov, AA.; Mascioli, K.; Beauchamp, GK. The molecular basis of the mammalian sweet tooth. In: Medeiros-Neto, G.; Halpern, A.; Bouchard, C., editors. Progress in Obesity Research. John Libbey Eurotext Ltd; London: 2003. p. 304-306.
97. Reed DR, Bachmanov AA, Beauchamp GK, Tordoff MG, Price RA. Heritable variation in food preferences and their contribution to obesity. Behav Genet. 1997; 27:373–387. [PubMed: 9519563]
98. Reed DR, Tanaka T, McDaniel AH. Diverse tastes: Genetics of sweet and bitter perception. Physiol Behav. 2006; 88:215–26. [PubMed: 16782140]
99. Drayna D. Human taste genetics. Annu Rev Genomics Hum Genet. 2005; 6:217–35. [PubMed: 16124860]
100. Kim UK, Breslin PA, Reed D, Drayna D. Genetics of human taste perception. J Dent Res. 2004; 83:448–53. [PubMed: 15153450]
101. Lugaz O, Pillias AM, Faurion A. A new specific ageusia: some humans cannot taste L-glutamate. Chem Senses. 2002; 27:105–15. [PubMed: 11839608]
102. Fushan AA, Simons CT, Slack JP, Manichaikul A, Drayna D. Allelic polymorphism within the TAS1R3 promoter is associated with human taste sensitivity to sucrose. Curr Biol. 2009; 19:1288–93. [PubMed: 19559618]
103. Eny KM, Wolever TM, Corey PN, El-Sohemy A. Genetic variation in TAS1R2 (Ile191Val) is associated with consumption of sugars in overweight and obese individuals in 2 distinct populations. Am J Clin Nutr. 2010; 92:1501–10. [PubMed: 20943793]
104. Chen QY, Alarcon S, Tharp A, et al. Perceptual variation in umami taste and polymorphisms in TAS1R taste receptor genes. Am J Clin Nutr. 2009; 90:770S–779S. [PubMed: 19587085]
105. Raliou M, Boucher Y, Wiencis A, et al. Tas1R1-Tas1R3 taste receptor variants in human fungiform papillae. Neurosci Lett. 2009; 451:217–21. [PubMed: 19146926]
106. Shigemura N, Shirosaki S, Sanematsu K, Yoshida R, Ninomiya Y. Genetic and molecular basis of individual differences in human umami taste perception. PLoS One. 2009; 4:e6717. [PubMed: 19696921]
107. Fuller JL. Single-locus control of saccharin preference in mice. J Hered. 1974; 65:33–36. [PubMed: 4847746]
108. Lush IE. The genetics of tasting in mice. VI. Saccharin, acesulfame, dulcin and sucrose. Genet Res. 1989; 53:95–99. [PubMed: 2744455]
109. Lush IE, Hornigold N, King P, Stoye JP. The genetics of tasting in mice. VII. Glycine revisited, and the chromosomal location of *Sac* and *Soa*. Genet Res. 1995; 66:167–174. [PubMed: 8522158]
110. Belknap JK, Crabbe JC, Plomin R, et al. Single-locus control of saccharin intake in BXD/Ty recombinant inbred (RI) mice: Some methodological implications for RI strain analysis. Behav Genet. 1992; 22:81–100. [PubMed: 1590732]
111. Bachmanov AA, Li X, Reed DR, et al. Positional cloning of the mouse saccharin preference (*Sac*) locus. Chem Senses. 2001; 26:925–933. [PubMed: 11555487]
112. Li X, Bachmanov AA, Li S, et al. Genetic, physical and comparative map of the subtelomeric region of mouse chromosome 4. Mamm Genome. 2002; 13:5–19. [PubMed: 11773963]
113. Nie Y, Vigues S, Hobbs JR, Conn GL, Munger SD. Distinct contributions of T1R2 and T1R3 taste receptor subunits to the detection of sweet stimuli. Curr Biol. 2005; 15:1948–52. [PubMed: 16271873]

114. Inoue M, Reed DR, Li X, et al. Allelic variation of the Tas1r3 taste receptor gene selectively affects behavioral and neural taste responses to sweeteners in the F2 hybrids between C57BL/6ByJ and 129P3/J mice. J Neurosci. 2004; 24:2296–303. [PubMed: 14999080]
115. Inoue M, Glendinning JI, Theodorides ML, et al. Allelic variation of the Tas1r3 taste receptor gene selectively affects taste responses to sweeteners: evidence from 129. B6-Tas1r3 congenic mice Physiol Genomics. 2007; 32:82–94. [PubMed: 17911381]
116. Zukerman S, Glendinning JI, Margolskee RF, Sclafani A. T1R3 taste receptor is critical for sucrose but not Polycose taste. Am J Physiol Regul Integr Comp Physiol. 2009; 296:R866–76. [PubMed: 19091911]
117. Treesukosol Y, Blonde GD, Spector AC. T1R2 and T1R3 subunits are individually unnecessary for normal affective licking responses to Polycose: implications for saccharide taste receptors in mice. Am J Physiol Regul Integr Comp Physiol. 2009; 296:R855–65. [PubMed: 19158407]
118. Sclafani A. The sixth taste? Appetite. 2004; 43:1–3. [PubMed: 15262010]
119. Glendinning JI. Is the bitter rejection response always adaptive? Physiol Behav. 1994; 56:1217–27. [PubMed: 7878094]
120. Adler E, Hoon MA, Mueller KL, et al. A novel family of mammalian taste receptors. Cell. 2000; 100:693–702. [PubMed: 10761934]
121. Chandrashekar J, Mueller KL, Hoon MA, et al. T2Rs function as bitter taste receptors. Cell. 2000; 100:703–711. [PubMed: 10761935]
122. Matsunami H, Montmayeur JP, Buck LB. A family of candidate taste receptors in human and mouse. Nature. 2000; 404:601–604. [PubMed: 10766242]
123. Mueller KL, Hoon MA, Erlenbach I, et al. The receptors and coding logic for bitter taste. Nature. 2005; 434:225–9. [PubMed: 15759003]
124. Chandrashekar J, Hoon MA, Ryba NJ, Zuker CS. The receptors and cells for mammalian taste. Nature. 2006; 444:288–94. [PubMed: 17108952]
125. Behrens M, Foerster S, Staehler F, Raguse JD, Meyerhof W. Gustatory expression pattern of the human TAS2R bitter receptor gene family reveals a heterogenous population of bitter responsive taste receptor cells. J Neurosci. 2007; 27:12630–40. [PubMed: 18003842]
126. Spector AC, Kopka SL. Rats fail to discriminate quinine from denatonium: implications for the neural coding of bitter-tasting compounds. J Neurosci. 2002; 22:1937–41. [PubMed: 11880524]
127. Aspen J, Gatch MB, Woods JH. Training and characterization of a quinine taste discrimination in rhesus monkeys. Psychopharmacology (Berl). 1999; 141:251–7. [PubMed: 10027506]
128. Chan CY, Yoo JE, Travers SP. Diverse bitter stimuli elicit highly similar patterns of Fos-like immunoreactivity in the nucleus of the solitary tract. Chem Senses. 2004; 29:573–81. [PubMed: 15337683]
129. Scott TR, Giza BK, Yan J. Gustatory neural coding in the cortex of the alert cynomolgus macaque: the quality of bitterness. J Neurophysiol. 1999; 81:60–71. [PubMed: 9914267]
130. Caicedo A, Roper SD. Taste receptor cells that discriminate between bitter stimuli. Science. 2001; 291:1557–60. [PubMed: 11222863]
131. Dahl M, Erickson RP, Simon SA. Neural responses to bitter compounds in rats. Brain Res. 1997; 756:22–34. [PubMed: 9187310]
132. Frank ME, Bouverat BP, MacKinnon BI, Hettinger TP. The distinctiveness of ionic and nonionic bitter stimuli. Physiol Behav. 2004; 80:421–31. [PubMed: 14741226]
133. Meyerhof W, Batram C, Kuhn C, et al. The molecular receptive ranges of human TAS2R bitter taste receptors. Chem Senses. 2010; 35:157–70. [PubMed: 20022913]
134. Behrens M, Meyerhof W. Bitter taste receptors and human bitter taste perception. Cell Mol Life Sci. 2006; 63:1501–9. [PubMed: 16732425]
135. Kim UK, Drayna D. Genetics of individual differences in bitter taste perception: lessons from the PTC gene. Clin Genet. 2005; 67:275–80. [PubMed: 15733260]
136. Kim U, Wooding S, Ricci D, Jorde LB, Drayna D. Worldwide haplotype diversity and coding sequence variation at human bitter taste receptor loci. Hum Mutat. 2005; 26:199–204. [PubMed: 16086309]

137. Meyerhof W. Elucidation of mammalian bitter taste. Rev Physiol Biochem Pharmacol. 2005; 154:37–72. [PubMed: 16032395]

138. Sawano S, Seto E, Mori T, Hayashi Y. G-protein-dependent and -independent pathways in denatonium signal transduction. Biosci Biotechnol Biochem. 2005; 69:1643–51. [PubMed: 16195580]

139. Lindemann B. Taste reception. Physiol Rev. 1996; 76:719–766.

140. Rosenzweig S, Yan W, Dasso M, Spielman AI. Possible novel mechanism for bitter taste mediated through cGMP. J Neurophysiol. 1999; 81:1661–5. [PubMed: 10200202]

141. Takeuchi H, Tsunenari T, Kurahashi T, Kaneko A. Physiology of morphologically identified cells of the bullfrog fungiform papilla. Neuroreport. 2001; 12:2957–62. [PubMed: 11588610]

142. Jacobs WW. Taste responses in wild and domestic guinea pigs. Physiol Behav. 1978; 20:579–588. [PubMed: 684093]

143. Glendinning JI. Is the bitter rejection response always adaptive? Physiol Behav. 1994; 56:1217–1227. [PubMed: 7878094]

144. Nolte DL, Mason JR, Lewis SL. Tolerance of bitter compounds by an herbivore, *Cavia porcellus*. J Chem Ecol. 1994; 20:303–308. [PubMed: 24242055]

145. Field KL, Bachmanov AA, Mennella JA, Beauchamp GK, Kimball BA. Protein hydrolysates are avoided by herbivores but not by omnivores in two-choice preference tests. PLoS One. 2009; 4:e4126. [PubMed: 19122811]

146. Field KL, Beauchamp GK, Kimball BA, Mennella JA, Bachmanov AA. Bitter avoidance in guinea pigs (Cavia porcellus) and mice (Mus musculus and Peromyscus leucopus). J Comp Psychol. 2010; 124:455–9. [PubMed: 21090891]

147. Nelson TM, Munger SD, Boughter JD Jr. Taste sensitivities to PROP and PTC vary independently in mice. Chem Senses. 2003; 28:695–704. [PubMed: 14627538]

148. Bachmanov AA, Beauchamp GK. Taste Receptor Genes. Annu Rev Nutr. 2007; 27:389–414. [PubMed: 17444812]

149. Bufe B, Hofmann T, Krautwurst D, Raguse JD, Meyerhof W. The human TAS2R16 receptor mediates bitter taste in response to beta-glucopyranosides. Nat Genet. 2002; 32:397–401. [PubMed: 12379855]

150. Bufe B, Breslin PA, Kuhn C, et al. The molecular basis of individual differences in phenylthiocarbamide and propylthiouracil bitterness perception. Curr Biol. 2005; 15:322–7. [PubMed: 15723792]

151. Wooding S, Bufe B, Grassi C, et al. Independent evolution of bitter-taste sensitivity in humans and chimpanzees. Nature. 2006; 440:930–4. [PubMed: 16612383]

152. Go Y. Lineage-specific expansions and contractions of the bitter taste receptor gene repertoire in vertebrates. Mol Biol Evol. 2006; 23:964–72. [PubMed: 16484289]

153. Shi P, Zhang J, Yang H, Zhang YP. Adaptive diversification of bitter taste receptor genes in Mammalian evolution. Mol Biol Evol. 2003; 20:805–14. [PubMed: 12679530]

154. Conte C, Ebeling M, Marcuz A, Nef P, Andres-Barquin PJ. Evolutionary relationships of the Tas2r receptor gene families in mouse and human. Physiol Genomics. 2003; 14:73–82. [PubMed: 12734386]

155. Liman ER. Use it or lose it: molecular evolution of sensory signaling in primates. Pflugers Arch. 2006; 453:125–31. [PubMed: 16897042]

156. Ueda T, Ugawa S, Ishida Y, et al. Identification of coding single-nucleotide polymorphisms in human taste receptor genes involving bitter tasting. Biochem Biophys Res Commun. 2001; 285:147–51. [PubMed: 11437385]

157. Wang X, Thomas SD, Zhang J. Relaxation of selective constraint and loss of function in the evolution of human bitter taste receptor genes. Hum Mol Genet. 2004; 13:2671–8. [PubMed: 15367488]

158. Guo SW, Reed DR. The genetics of phenylthiocarbamide perception. Ann Hum Biol. 2001; 28:111–42. [PubMed: 11293722]

159. Kim UK, Jorgenson E, Coon H, et al. Positional cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide. Science. 2003; 299:1221–5. [PubMed: 12595690]

160. Drayna D, Coon H, Kim UK, et al. 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. 2003; 112:567–72. [PubMed: 12624758]

161. Prodi DA, Drayna D, Forabosco P, et al. Bitter taste study in a sardinian genetic isolate supports the association of phenylthiocarbamide sensitivity to the TAS2R38 bitter receptor gene. Chem Senses. 2004; 29:697–702. [PubMed: 15466815]

162. Mennella JA, Pepino MY, Reed DR. Genetic and environmental determinants of bitter perception and sweet preferences. Pediatrics. 2005; 115:e216–22. [PubMed: 15687429]

163. Duffy VB, Davidson AC, Kidd JR, et al. Bitter receptor gene (TAS2R38), 6-n-propylthiouracil (PROP) bitterness and alcohol intake. Alcohol Clin Exp Res. 2004; 28:1629–37. [PubMed: 15547448]

164. Sandell MA, Breslin PA. Variability in a taste-receptor gene determines whether we taste toxins in food. Curr Biol. 2006; 16:R792–4. [PubMed: 16979544]

165. Wooding S, Kim UK, Bamshad MJ, et al. Natural selection and molecular evolution in PTC, a bitter-taste receptor gene. Am J Hum Genet. 2004; 74:637–46. [PubMed: 14997422]

166. Soranzo N, Bufe B, Sabeti PC, et al. Positive selection on a high-sensitivity allele of the human bitter-taste receptor TAS2R16. Curr Biol. 2005; 15:1257–65. [PubMed: 16051168]

167. Roudnitzky N, Bufe B, Thalmann S, et al. Genomic, genetic and functional dissection of bitter taste responses to artificial sweeteners. Hum Mol Genet. 2011; 20:3437–49. [PubMed: 21672920]

168. Reed DR, Zhu G, Breslin PA, et al. The perception of quinine taste intensity is associated with common genetic variants in a bitter receptor cluster on chromosome 12. Hum Mol Genet. 2010; 19:4278–85. [PubMed: 20675712]

169. Nelson TM, Munger SD, Boughter JD Jr. Haplotypes at the Tas2r locus on distal chromosome 6 vary with quinine taste sensitivity in inbred mice. BMC Genet. 2005; 6:32. [PubMed: 15938754]

170. Boughter JD Jr, Raghow S, Nelson TM, Munger SD. Inbred mouse strains C57BL/6J and DBA/2J vary in sensitivity to a subset of bitter stimuli. BMC Genet. 2005; 6:36. [PubMed: 15967025]

171. Fitzsimons, JT. The Physiology of Thirst and Sodium Appetite. Cambridge University Press; Cambridge: 1979.

172. Denton, D. The hunger for salt: An anthropological, physiological and medical analysis. Springer-Verlag; Berlin: 1984.

173. Beauchamp, GK.; Stein, LJ. Salt Taste. In: Firestein, S.; Beauchamp, GK., editors. Olfaction and Taste. Elsevier/Academic Press; San Diego: 2008. p. 401-408.

174. Schiffman S, Lockhead E, Mars F. Amiloride reduces the taste intensity of Na+ and Li+ salts and sweeteners. Proc Natl Acad Sci USA. 1983; 80:6136–6140. [PubMed: 6577473]

175. Heck GL, Mierson S, DeSimone JA. Salt taste transduction occurs through an amiloride-sensitive sodium transport pathway. Science. 1984; 223:403–405. [PubMed: 6691151]

176. Brand J, Teeter J, Silver W. Inhibition by amiloride of chorda tympani responses evoked by monovalent salts. Brain Res. 1985; 334:207–214. [PubMed: 3995317]

177. Kellenberger S, Schild L. Epithelial sodium channel/degenerin family of ion channels: a variety of functions for a shared structure. Physiol Rev. 2002; 82:735–67. [PubMed: 12087134]

178. Bachmanov AA, Li X, Reed DR, et al. Positional cloning of the mouse saccharin preference (*Sac*) locus. Chem Senses. 2001; 26:925–33. [PubMed: 11555487]

179. Li XJ, Blackshaw S, Snyder SH. Expression and localization of amiloride-sensitive sodium channel indicate a role for non-taste cells in taste perception. Proc Natl Acad Sci USA. 1994; 91:1814–8. [PubMed: 8127886]

180. Lindemann B, Barbry P, Kretz O, Bock R. Occurrence of ENaC subunit mRNA and immunocytochemistry of the channel subunits in taste buds of the rat vallate papilla. Ann N Y Acad Sci. 1998; 855:116–27. [PubMed: 9929592]

181. Kretz O, Barbry P, Bock R, Lindemann B. Differential expression of RNA and protein of the three pore-forming subunits of the amiloride-sensitive epithelial sodium channel in taste buds of the rat. J Histochem Cytochem. 1999; 47:51–64. [PubMed: 9857212]
182. Lin W, Finger TE, Rossier BC, Kinnamon SC. Epithelial Na+ channel subunits in rat taste cells: localization and regulation by aldosterone. J Comp Neurol. 1999; 405:406–20. [PubMed: 10076935]
183. Lindemann B. Sodium taste. Curr Opin Nephrol Hypertens. 1997; 6:425–9. [PubMed: 9327199]
184. Halpern BP. Amiloride and vertebrate gustatory responses to NaCl. Neurosci Biobehav Rev. 1998; 23:5–47. [PubMed: 9861611]
185. Boughter JD Jr, Gilbertson TA. From channels to behavior: an integrative model of NaCl taste. Neuron. 1999; 22:213–5. [PubMed: 10069327]
186. Bosak, N.; Inoue, M.; Nelson, T., et al. Epithelial sodium channel (ENaC) is involved in reception of sodium taste: evidence from mice with a tissue-specific conditional targeted mutation of the ENaCa gene (Abstract). Chem Senses; AChemS XXXII Annual Meeting; 2010 April 21–25; St. Petersburg (FL). 2010.
187. Chandrashekar J, Kuhn C, Oka Y, et al. The cells and peripheral representation of sodium taste in mice. Nature. 2010; 464:297–301. [PubMed: 20107438]
188. Ye Q, Heck GL, DeSimone JA. Voltage dependence of the rat chorda tympani response to Na+ salts: implications for the functional organization of taste receptor cells. J Neurophysiol. 1993; 70:167–78. [PubMed: 8395573]
189. Mierson S, Olson MM, Tietz AE. Basolateral amiloride-sensitive Na+ transport pathway in rat tongue epithelium. J Neurophysiol. 1996; 76:1297–309. [PubMed: 8871237]
190. Yoshida R, Horio N, Murata Y, et al. NaCl responsive taste cells in the mouse fungiform taste buds. Neuroscience. 2009; 159:795–803. [PubMed: 19167465]
191. Formaker BK, Hill DL. An analysis of residual NaCl taste response after amiloride. Am J Physiol. 1988; 255:R1002–7. [PubMed: 3202215]
192. Elliott EJ, Simon SA. The anion in salt taste: a possible role of paracellular pathways. Brain Res. 1990; 535:9–17. [PubMed: 1963343]
193. Rehnberg BG, MacKinnon BI, Hettinger TP, Frank ME. Anion modulation of taste responses in sodium-sensitive neurons of the hamster chorda tympani nerve. J Gen Physiol. 1993; 101:453–65. [PubMed: 8473851]
194. Oka Y, Butnaru M, von Buchholtz L, Ryba NJ, Zuker CS. High salt recruits aversive taste pathways. Nature. 2013; 494:472–475. [PubMed: 23407495]
195. Caterina MJ, Schumacher MA, Tominaga M, et al. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature. 1997; 389:816–824. [PubMed: 9349813]
196. Lyall V, Heck GL, Vinnikova AK, et al. The mammalian amiloride-insensitive non-specific salt taste receptor is a vanilloid receptor-1 variant. J Physiol. 2004; 558:147–59. [PubMed: 15146042]
197. Ruiz C, Gutknecht S, Delay E, Kinnamon S. Detection of NaCl and KCl in TRPV1 knockout mice. Chem Senses. 2006; 31:813–20. [PubMed: 16923776]
198. Treesukosol Y, Lyall V, Heck GL, DeSimone JA, Spector AC. A psychophysical and electrophysiological analysis of salt taste in Trpv1 null mice. Am J Physiol Regul Integr Comp Physiol. 2007; 292:R1799–809. [PubMed: 17234959]
199. Breza JM, Contreras RJ. Anion size modulates salt taste in rats. J Neurophysiol. 2012; 107:1632–48. [PubMed: 22205652]
200. Smith KR, Treesukosol Y, Paedae AB, Contreras RJ, Spector AC. Contribution of the TRPV1 channel to salt taste quality in mice as assessed by conditioned taste aversion generalization and chorda tympani nerve responses. Am J Physiol Regul Integr Comp Physiol. 2012; 303:R1195–205. [PubMed: 23054171]
201. Kido MA, Muroya H, Yamaza T, Terada Y, Tanaka T. Vanilloid receptor expression in the rat tongue and palate. J Dent Res. 2003; 82:393–7. [PubMed: 12709508]
202. Ishida Y, Ugawa S, Ueda T, Murakami S, Shimada S. Vanilloid receptor subtype-1 (VR1) is specifically localized to taste papillae. Brain Res Mol Brain Res. 2002; 107:17–22. [PubMed: 12414119]

203. Moon YW, Lee JH, Yoo SB, Jahng JW. Capsaicin receptors are colocalized with sweet/bitter receptors in the taste sensing cells of circumvallate papillae. Genes Nutr. 2010; 5:251–5. [PubMed: 20016958]
204. Riera CE, Vogel H, Simon SA, le Coutre J. Artificial sweeteners and salts producing a metallic taste sensation activate TRPV1 receptors. Am J Physiol Regul Integr Comp Physiol. 2007; 293:R626–34. [PubMed: 17567713]
205. Moyer, B.; Zlotnik, A.; Hevezi, P., et al. Identification of TRPML3 (MCOLN3) as a Salty Taste Receptor and Use in Assays for Identifying Taste (Salty) Modulators and/or Therapeutics that Modulate Sodium Transport, Absorption or Excretion and/or Aldosterone and/or Vasopressin Production or Release. Patent Pub No. WO/2009/008950.. 2009.
206. Castiglioni AJ, Remis NN, Flores EN, Garcia-Anoveros J. Expression and vesicular localization of mouse Trpml3 in stria vascularis, hair cells, and vomeronasal and olfactory receptor neurons. J Comp Neurol. 2011; 519:1095–114. [PubMed: 21344404]
207. Ossebaard CA, Polet IA, Smith DV. Amiloride effects on taste quality: comparison of single and multiple response category procedures. Chem Senses. 1997; 22:267–75. [PubMed: 9218139]
208. Huque T, Cowart BJ, Dankulich-Nagrudny L, et al. Sour ageusia in two individuals implicates ion channels of the ASIC and PKD families in human sour taste perception at the anterior tongue. PLoS One. 2009; 4:e7347. [PubMed: 19812697]
209. Stähler F, Riedel K, Demgensky S, et al. A role of the epithelial sodium channel in human salt taste transduction? Chemosensory Perception. 2008; 1:78–90.
210. Brand, JG.; Huque, T. Human salty taste receptor and methods of modulating salty taste perception. 2008 Patent Pub No. WO2008051447 A2.
211. Ji HL, Zhao RZ, Chen ZX, et al. delta ENaC: a novel divergent amiloride-inhibitable sodium channel. Am J Physiol Lung Cell Mol Physiol. 2012; 303:L1013–26. [PubMed: 22983350]
212. Giraldez T, Rojas P, Jou J, Flores C, Alvarez de la Rosa D. The epithelial sodium channel delta-subunit: new notes for an old song. Am J Physiol Renal Physiol. 2012; 303:F328–38. [PubMed: 22573384]
213. Hellekant G, Ninomiya Y, Danilova V. Taste in chimpanzees II: single chorda tympani fibers. Physiol Behav. 1997; 61:829–41. [PubMed: 9177554]
214. Danilova V, Danilov Y, Roberts T, et al. Sense of taste in a new world monkey, the common marmoset: recordings from the chorda tympani and glossopharyngeal nerves. J Neurophysiol. 2002; 88:579–94. [PubMed: 12163511]
215. Eylam S, Spector AC. Oral amiloride treatment decreases taste sensitivity to sodium salts in C57BL/6J and DBA/2J mice. Chem Senses. 2003; 28:447–58. [PubMed: 12826540]
216. Liu L, Leonard AS, Motto DG, et al. Contribution of Drosophila DEG/ENaC genes to salt taste. Neuron. 2003; 39:133–46. [PubMed: 12848938]
217. Ishiwatari Y, Bachmanov AA. NaCl taste thresholds in 13 inbred mouse strains. Chem Senses. 2012; 37:497–508. [PubMed: 22293936]
218. Shigemura N, Ohkuri T, Sadamitsu C, et al. Amiloride-sensitive NaCl taste responses are associated with genetic variation of ENaC α-subunit in mice. Am J Physiol Regul Integr Comp Physiol. 2008; 294:R66–R75. [PubMed: 17977920]
219. Dias AG, Rousseau D, Duizer L, et al. Genetic variation in putative salt taste receptors and salt taste perception in humans. Chem Senses. 2013; 38:137–45. [PubMed: 23118204]
220. Nelson TM, Lopezjimenez ND, Tessarollo L, et al. Taste function in mice with a targeted mutation of the *Pkd1l3* gene. Chem Senses. 2010; 35:565–77. [PubMed: 20605874]
221. Ishimaru Y, Inada H, Kubota M, et al. Transient receptor potential family members PKD1L3 and PKD2L1 form a candidate sour taste receptor. Proc Natl Acad Sci USA. 2006; 103:12569–74. [PubMed: 16891422]
222. Huang AL, Chen X, Hoon MA, et al. The cells and logic for mammalian sour taste detection. Nature. 2006; 442:934–8. [PubMed: 16929298]
223. LopezJimenez ND, Sainz E, Cavenagh MM, et al. Two novel genes, Gpr113, which encodes a family 2 G-protein-coupled receptor, and Trcg1, are selectively expressed in taste receptor cells. Genomics. 2005; 85:472–82. [PubMed: 15780750]

224. Horio N, Yoshida R, Yasumatsu K, et al. Sour taste responses in mice lacking PKD channels. PLoS One. 2011; 6:e20007. [PubMed: 21625513]

225. Wise PM, Hansen JL, Reed DR, Breslin PA. Twin study of the heritability of recognition thresholds for sour and salty taste. Chem Senses. 2007; 32:749–54. [PubMed: 17623712]

226. Bachmanov AA, Tordoff MG, Beauchamp GK. Acid acceptance in 28 mouse strains (Abstract). Chem Senses. 2000; 25:600.

227. Gilbertson TA, Baquero AF, Spray-Watson KJ. Water taste: the importance of osmotic sensing in the oral cavity. J Water Health. 2006; 4(Suppl 1):35–40. [PubMed: 16493898]

228. Gilbertson TA, Kim I, Siears NL, Zhang H, Liu L. The water response in taste cells: expression of aquaporin-1, -2 and -5 and the characterization of hypoosmic-induced currents in mammalian taste cells (Abstract). Chem Senses. 1999; 24:596.

229. Bartoshuk LM. NaCl thresholds in man: thresholds for water taste or NaCl taste? J Comp Physiol Psychol. 1974; 87:310–25. [PubMed: 4430743]

230. Bartoshuk, LM. Water taste in mammals. In: Weijnen, JAWM.; Mendelson, J., editors. Drinking behavior: oral stimulation, reinforcement, and preference. Plenum Press; New York: 1977. p. 317-339.

231. Bartoshuk LM, McBurney DH, Pfaffmann C. Taste of sodium chloride solutions after adaptation to sodium chloride: implications for the “water taste”. Science. 1964; 143:967–8. [PubMed: 14090150]

232. McBurney, DH.; Bartoshuk, LM. Water taste in mammals. In: Schneider, D., editor. Olfaction and Taste IV. Proceedings of the Fourth International Symposium held in Starnberg; Germany. August 2–4 1971; Stuttgart: Wissenschaftlische Verlagsgesellschaft MBH; 1972. p. 329-335.

233. DuBois GE. Unraveling the biochemistry of sweet and umami tastes. Proc Natl Acad Sci USA. 2004; 101:13972–3. [PubMed: 15383662]

234. Galindo-Cuspinera V, Winnig M, Bufe B, Meyerhof W, Breslin PA. A TAS1R receptor-based explanation of sweet ‘water-taste’. Nature. 2006; 441:354–7. [PubMed: 16633339]

235. Bachmanov AA, Kiefer SW, Molina JC, et al. Chemosensory factors influencing alcohol perception, preferences, and consumption. Alcohol Clin Exp Res. 2003; 27:220–31. [PubMed: 12605071]

236. Bachmanov AA, Reed DR, Li X, et al. Voluntary ethanol consumption by mice: genome-wide analysis of quantitative trait loci and their interactions in a C57BL/6ByJ x 129P3/J F2 intercross. Genome Res. 2002; 12:1257–68. [PubMed: 12176933]

237. Hinrichs AL, Wang JC, Bufe B, et al. Functional variant in a bitter-taste receptor (hTAS2R16) influences risk of alcohol dependence. Am J Hum Genet. 2006; 78:103–11. [PubMed: 16385453]

238. Dunkel A, Koster J, Hofmann T. Molecular and sensory characterization of gamma-glutamyl peptides as key contributors to the kokumi taste of edible beans (*Phaseolus vulgaris L.*) J Agric Food Chem. 2007; 55:6712–9. [PubMed: 17616213]

239. Ueda Y, Yonemitsu M, Tsubuku T, Sakaguchi M, Miyajima R. Flavor characteristics of glutathione in raw and cooked foodstuffs. Biosci Biotechnol Biochem. 1997; 61:1977–80. [PubMed: 9438977]

240. Ohsu T, Amino Y, Nagasaki H, et al. Involvement of the calcium-sensing receptor in human taste perception. J Biol Chem. 2010; 285:1016–22. [PubMed: 19892707]

241. San Gabriel A, Uneyama H, Maekawa T, Torii K. The calcium-sensing receptor in taste tissue. Biochem Biophys Res Commun. 2009; 378:414–8. [PubMed: 19056349]

242. Maruyama Y, Yasuda R, Kuroda M, Eto Y. Kokumi substances, enhancers of basic tastes, induce responses in calcium-sensing receptor expressing taste cells. PLoS One. 2012; 7:e34489. [PubMed: 22511946]

243. Tordoff MG. Calcium: taste, intake, and appetite. Physiol Rev. 2001; 81:1567–97. [PubMed: 11581497]

244. Tordoff MG, Shao H, Alarcon LK, et al. Involvement of T1R3 in calcium-magnesium taste. Physiol Genomics. 2008; 34:338–48. [PubMed: 18593862]

245. Tordoff MG, Alarcon LK, Valmeki S, Jiang P. T1R3: a human calcium taste receptor. Sci Rep. 2012; 2:496. [PubMed: 22773945]

246. Fukuwatari T, Kawada T, Tsuruta M, et al. Expression of the putative membrane fatty acid transporter (FAT) in taste buds of the circumvallate papillae in rats. FEBS Lett. 1997; 414:461–4. [PubMed: 9315741]

247. Zhang X, Fitzsimmons RL, Cleland LG, et al. CD36/fatty acid translocase in rats: distribution, isolation from hepatocytes, and comparison with the scavenger receptor SR-B1. Lab Invest. 2003; 83:317–32. [PubMed: 12649333]

248. Laugerette F, Passilly-Degrace P, Patris B, et al. CD36 involvement in orosensory detection of dietary lipids, spontaneous fat preference, and digestive secretions. J Clin Invest. 2005; 115:3177–84. [PubMed: 16276419]

249. Cartoni C, Yasumatsu K, Ohkuri T, et al. Taste preference for fatty acids is mediated by GPR40 and GPR120. J Neurosci. 2010; 30:8376–82. [PubMed: 20573884]

250. Matsumura S, Mizushige T, Yoneda T, et al. GPR expression in the rat taste bud relating to fatty acid sensing. Biomed Res. 2007; 28:49–55. [PubMed: 17379957]

251. Gaillard D, Laugerette F, Darcel N, et al. The gustatory pathway is involved in CD36-mediated orosensory perception of long-chain fatty acids in the mouse. FASEB J. 2008; 22:1458–68. [PubMed: 18162488]

252. El-Yassimi A, Hichami A, Besnard P, Khan NA. Linoleic acid induces calcium signaling, Src kinase phosphorylation, and neuro-transmitter release in mouse CD36-positive gustatory cells. J Biol Chem. 2008; 283:12949–59. [PubMed: 18321850]

253. Sclafani A, Ackroff K, Abumrad NA. CD36 gene deletion reduces fat preference and intake but not post-oral fat conditioning in mice. Am J Physiol Regul Integr Comp Physiol. 2007; 293:R1823–32. [PubMed: 17804586]

254. Galindo MM, Voigt N, Stein J, et al. G protein-coupled receptors in human fat taste perception. Chem Senses. 2012; 37:123–39. [PubMed: 21868624]

255. Pepino MY, Love-Gregory L, Klein S, Abumrad NA. The fatty acid translocase gene CD36 and lingual lipase influence oral sensitivity to fat in obese subjects. J Lipid Res. 2012; 53:561–6. [PubMed: 22210925]

256. Keller KL, Liang LC, Sakimura J, et al. Common variants in the CD36 gene are associated with oral fat perception, fat preferences, and obesity in African Americans. Obesity (Silver Spring). 2012; 20:1066–73. [PubMed: 22240721]

257. Bachmanov, AA. Genetic architecture of sweet taste. In: Weerasinghe, DK.; DuBois, GE., editors. Sweetness and Sweeteners: Biology, Chemistry and Psychophysics. American Chemical Society; Washington, D.C: 2008. p. 18-47.

258. Shi P, Zhang J. Extraordinary diversity of chemosensory receptor gene repertoires among vertebrates. Results Probl Cell Differ. 2009; 47:57–75. [PubMed: 19083127]

259. Dong D, Jones G, Zhang S. Dynamic evolution of bitter taste receptor genes in vertebrates. BMC Evol Biol. 2009; 9:12. [PubMed: 19144204]

260. Davis JK, Lowman JJ, Thomas PJ, et al. Evolution of a bitter taste receptor gene cluster in a New World sparrow. Genome Biol Evol. 2010; 2:358–70. [PubMed: 20624740]

261. Zhou Y, Dong D, Zhang S, Zhao H. Positive selection drives the evolution of bat bitter taste receptor genes. Biochem Genet. 2009; 47:207–15. [PubMed: 19242789]

262. Oike H, Nagai T, Furuyama A, et al. Characterization of ligands for fish taste receptors. J Neurosci. 2007; 27:5584–92. [PubMed: 17522303]

263. Kusuhara Y, Yoshida R, Ohkuri T, Yasumatsu K, Voigt A, Hubner S, Maeda K, Boehm U, Meyerhof W, Ninomiya Y. Taste responses in mice lacking taste receptor subunit T1R1. J Physiol. 2013; 591:1967–1985. [PubMed: 23339178]

264. Ohmoto M, Okada S, Nakamura S, Abe K, Matsumoto I. Mutually exclusive expression of Gaia and Ga14 reveales diversification of taste receptor cells in zebrafish. J Comp Neurol. 2011; 519:1616–1629. [PubMed: 21452212]

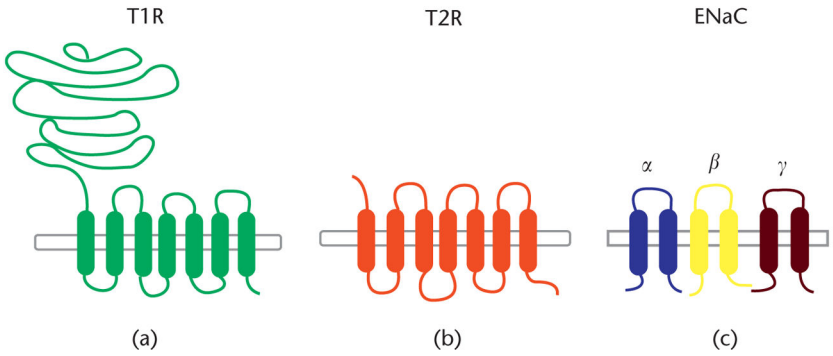

Fig. (1).

Known taste receptors. The T1R (**a**; sweet and umami) and T2R (**b**; bitter) proteins are G protein-coupled receptors, while ENaC (**c**; salty) is an ion channel. Reproduced from [6] by permission of John Wiley & Sons, Ltd.

Table 1

Numbers of T1R genes in vertebrates.

Species	T1R1	T1R2	T1R3
Mammals			
Human (*Homo sapiens*)	1	1	1
Mouse (*Mus musculus*)	1	1	1
Rat (*Rattus norvegicus*)	1	1	1
Dog (*Canis familiaris*)	1	1	1
Opossum (*Monodelphis domestica*)	1	1	1
Pig (*Sus scrofa*)	1		1
Horse (*Equus caballus*)		0	
Giant panda (*Ailuropoda melanoleuca*)	0 (1)		
Bats*	0 (1)	1	1
Vampire bats**	0 (1)	0 (1)	0 (1)
Spotted seal (*Phoca largha*)	0 (1)		
Harbor seal (*Phoca vitulina*)	0 (1)		
Caspian seal (*Pusa caspica*)	0 (1)		
Northern elephant seal (*Mirounga angustirostris*)	0 (1)		
Australian sea lion (*Neophoca cinerea*)	0 (1)		
South American sea lion (*Otaria byronia*)	0 (1)		
Domestic cat (*Felis silvestris catus*)	1	0 (1)	1
Tiger (*Panthera tigris*)		0 (1)	
Cheetah (*Acinonyx jubatus*)		0 (1)	
Asiatic lion (*Panthera leo persica*)		0 (1)	
Southern fur seal (*Arctocephalus forsteri*)		0 (1)	
Pacific harbor seal (*Phoca vitulina richardii*)		0 (1)	
Asian small-clawed otter (*Amblonyx cinereus*)		0 (1)	
Spotted hyena (*Crocuta crocuta*)		0 (1)	
Fossa (*Cryptoprocta ferox*)		0 (1)	
Banded linsang (*Prionodon linsang*)		0 (1)	
Bottlenose dolphin (*Tursiops truncates*)	0 (1)	0 (1)	0 (1)
California sea lion (*Zalophus californianus californianus*)	0 (1)	0 (1)	0 (1)
Birds			
Zebra finch (*Taeniopygia guttata*)		0	
Chicken (*Gallus gallus*)	1	0	1
Amphibian			
Western clawed frog (*Xenopus tropicalis*)	0	0	0
Fish			
Fugu (*Takifugu rubripes*)	1	2	1

Species	T1R1	T1R2	T1R3
Pufferfish (*Tetraodon nigroviridis*)	1	3	1
Zebrafish (*Danio rerio*)	1	2	1
Medaka (*Oryzias latipes*)	1	3	1

Data are from [5, 62, 68, 70, 73, 257, 258].

Numbers reflect functional and putatively functional genes (pseudogenes). Partial genes are considered putatively functional. When different sources indicate different numbers of genes, the highest estimate is shown. Empty cells indicate lack of data.

* Multiple (n=28) species, excluding vampire bats [68].

** Three species of vampire bats [68].

Table 2

Numbers of T2R genes in vertebrates

Species	Functional and putatively functional genes	Pseudogenes
Mammals		
Human (*Homo sapiens*)	28	16
Macaque (*Macaca mulatta*)	27	11
Mouse (*Mus musculus*)	36	7
Rat (*Rattus norvegicus*)	37	7
Cow (*Bos taurus*)	19	15
Horse (*Equus caballus*)	19	36
Dog (*Canis familiaris*)	16	5
Little brown bat (*Myotis lucifugus*)	17	9
Bottlenose dolphin (*Tursiops truncates*)	0	10
Opossum (*Monodelphis domestica*)	29	7
Platypus (*Ornithorhynchus anatinus*)	5	1
Birds		
White-throated sparrow (*Zonotrichia albicollis*)	19	1
Zebra finch (*Taeniopygia guttata*)	7	
Chicken (*Gallus gallus*)	3	0
Reptile		
Lizard (*Anolis carolinensis*)	39	10
Amphibian		
Western clawed frog (*Xenopus tropicals*)	52	14
Fish		
Fugu (*Takifugu rubripes*)	4	0
Pufferfish (*Tetraodon nigroviridis*)	6	0
Zebrafish (*Danio rerio*)	5	0
Medaka (*Oryzias latipes*)	1	0
Stickleback (*Gasterosteus aculeatus*)	3	0

Data from [5, 73, 258–262]. When different sources indicate different numbers of genes, the highest estimate is shown. The empty cell for zebra finch indicates lack of data.