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Diverse tastes: Genetics of sweet and bitter perception

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Abstract

Humans will eat almost anything, from caribou livers to rutabagas, but there are some types of foods, and their associated taste qualities, that are preferred by large groups of people regardless of culture or experience. When many choices are available, humans chose foods that taste good, that is, create pleasing sensations in the mouth. The concept of good taste for most people encompasses both flavor and texture of food, and these sensations merge with taste proper to form the concept of goodness. Although we acknowledge the universality of the goodness (sweet) or badness (bitter) of basic taste qualities, we also find that people differ, sometimes extremely so, in their ability to perceive and enjoy these qualities and, by extension, food and drink. The reasons for these differences among people are not clear but are probably due to a combination of experience beginning at an early age, perhaps in utero; learning, for example, as with conditioned taste aversions; sex and maturity; and perceptual differences that arise from genetic variation. In this review, we focus on individual variations that arise from genetic differences and review two domains of science: recent developments in the molecular biology of taste transduction, with a focus on the genes involved and second, studies that examine biological relatives to determine the heritability of taste perception. Because the receptors for sweet, savory (*umami*), and bitter have recently been discovered, we summarize what is known about their function by reviewing the effect of naturally occurring and man-made alleles of these receptors, their shape and function based on receptor modeling techniques, and how they differ across animal species that vary in their ability to taste certain qualities. We discuss this literature in the context of how taste genes may differ among people and give rise to individuated taste experience, and what is currently known about the genetic effects on taste perception in humans.

Keywords

Tas1r3; Tas1r2; TAS2R38; Receptor; Perception; Genotype; Preference

1. Introduction

People differ in their ability to perceive their environment, and individual differences in vision and hearing are routinely assessed and, when needed, people are given assistance to compensate for their deficiencies, i.e., they are offered eyeglasses or hearing aids. Compared with these two senses, individual differences in taste are given less attention, and are not assessed except in cases where people participate in a research study or have gone to their doctor with specific complaints about taste loss. Probably this lack of attention is due to the belief that having a below-average sense of taste is not as important as having below-average vision and hearing and also because there is no obvious medical way to ‘correct’ a person’s sense of taste. There are no ‘eye-glasses’ or ‘hearing-aid’ for the tongue and compensation for deficiencies in a person’s sense of taste is currently accomplished in the kitchen rather than in the doctor’s office.

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Although a neglected topic, several recent discoveries have focused our attention on taste variation among people, and a related issue, which is why and how animal species differ in taste perception. For instance, some people are sensitive to a group of bitter compounds while other people are much less sensitive. Likewise, some strains of mice are sweet-loving whereas other strains are less so, and along the same line, cats are indifferent to sweet whereas dogs are anything but. Both in the case of bitter taste perception in humans and in the case of species differences in sweet perception, the differences are due to genetic factors, recently shown to be alternative forms (i.e., alleles) of taste receptor genes (described in detail below). This new information has led us to consider how widespread and how extreme human differences in taste perception are, how much of the variation is due to genetics, and whether allelic differences in taste receptor genes and other proteins in the taste pathway are common and whether they have large effects on perception.

Therefore this review has two purposes: first, because genetic differences occur in genes, the templates for proteins and other molecules in the taste pathway, we review what is known about taste biology. A brief review of taste from the tongue to the brain is necessary because there have been recent important studies that have filled knowledge gaps, and this new information suggests additional ways that individual differences might arise. In the second section, we examine sweetness, and then bitterness, dividing the recent research into receptors and their location, naturally occurring alleles, heterologous expression systems, modeling, nerves and brain, and comparisons among species; these topics are included because they are relevant to recent discoveries about individual differences in taste perception and because the topics themselves are often related. For instance, taste receptors have naturally occurring alleles that can be evaluated in a cell-based assay system (i.e., heterologous expression systems), and these alleles can also be used to predict how the receptor function will change using computer modeling, and then the DNA sequence can be compared across species to determine the origins in taste differences. In the last section, we discuss what is known about the genetics of human taste perception; first, we review the types of tests that have been used to assess human taste function, and how similar human family members, such as mother and children or twins, are to each other in the performance of these tests. These types of studies can provide an index of heritability. We then finish the review by discussing the small but growing number of studies which have examined the correlation between alleles of bitter taste receptors, disease and behavior in human subjects.

2. Taste biology

There are five modalities of taste that can be detected by most mammals: sweet, salt, sour, bitter, and umami [1–3]. For our ancestors, the ability to taste was important to ensure acquisition of nutrients and to avoid toxic substances. The liking for specific taste qualities is dependent on context and concentration: some taste qualities, such as sweet, are perceived as good and are, at least in the short term, benign at all concentrations. It can nonetheless be perceived by some as unpleasant at very high concentrations. Umami, the taste of monosodium glutamate thought to provide a signal for amino acid content, is pleasant, but only in some contexts, for instance, people do not like MSG when it is dissolved in plain water [4] but like soup better with MSG than without it [5]. Salt is good and desirable at low and moderate concentrations but is avoided at high concentrations unless the individual is salt or mineral deprived [6]. Sour also has a similar concentration–pleasantness relationship. Bitter is the opposite of sweet, assumed to be always bad at all concentrations; however, in practice humans do consume bitter foods and drinks—in most or all circumstances, the desired drug effects of the bitter compound may override the natural rejection response, for example, coffee or betel nuts. However it is possible that bitter may be pleasing without pairing with a drug, for instance, people in Asia eat bitter melon which has no obvious positive drug-like effects. In addition to these taste qualities, there may be a sixth taste, that for fats [7–9].

Taste perception starts on the tongue and soft palate, where specific chemicals in foods or drinks interact with taste receptors. These receptors are found on specialized epithelial cells called the taste receptor cells that neuron-like properties, including depolarization, release of neurotransmitters, and the ability to form a synapse to afferent neurons [1]. These taste receptor cells can be distinguished as type I, II, or III. Type I and type II cells stain differently during their histological preparation: type II cells are so-called 'light cells,' and type I cells are 'dark cells'. Type III cells synapse directly onto the afferent sensory fiber and are intermediate in appearance between light and dark cells. Taste receptor cells contain neuropeptides that may modify the activity of neighboring cells [10,11], and they communicate with afferent sensory nerves using ATP [12].

Approximately 50 to 150 taste cells organize into an onionlike configuration to form a taste bud. Taste buds are found distributed throughout the tongue on specialized structures called papillae, which have three types: fungiform, foliate, and circumvallate. Taste papillae on which most sweet receptors reside can be seen on the tip of the tongue and look like raised pink bumps or nipples (from which they derive their Latin name). The names of the individual papilla types also derive from their appearance: fungiform is related to fungi or mushroom-like, foliate papillae are so named because they look like folia or the pages of a book, and circumvallate translates roughly as 'surrounded with or as if with a rampart'. Taste buds are also located on the soft tissue of the mouth and upper throat.

Some textbooks present a rigid taste map in which only certain regions of the tongue are sensitive to certain taste qualities, but in fact, all tastants can be detected in most locations throughout the tongue. However, although in its most extreme representation the taste map is inaccurate, there are topographic locations that are more sensitive to certain tastants [13]. The expression of the relevant receptor proteins confirms these general observations from psychophysical analyses, for a review, see Ref. [14].

Three nerves carry information from the tongue to the brain: the chorda tympani (cranial nerve VII), which innervates the outer third of the tongue; the glossopharyngeal nerve (cranial nerve IX), which innervates the anterior two thirds of the tongue; and the nerve from the superficial petrosal branch (cranial nerve X; vagus), which innervates the larynx and the epiglottis (the flap that covers the trachea during swallowing so that food does not enter the lungs). Recordings of single nerve fibers from the chorda tympani of rats and mice indicate that fibers respond to more than one taste quality but that each fiber responds most vigorously to one quality above all others. For this reason, nerve fibers are often referred to as 'quality'-best, for example, sweet-best, in characterizing their response.

The primary taste areas in the lower brain are the nucleus of the solitary tract, parabrachial nucleus, and thalamic gustatory areas. How taste qualities map to these areas is not understood, but a recent study suggests that intermediate brain locations do maintain quality-dependent geography. For instance, most sweet-activated neurons map to the rostral fields of these regions [15].

How taste is coded and read by the brain is also not well understood, but there are two main hypotheses. One is the labeled-line theory, in which the signal from the taste receptor cells is carried without modification by neurons to the brain, where the direct line is read as a specific quality. In the other, cross-fiber or pattern hypothesis, the brain takes the pattern of nerve firing into account and then reads the more complex pattern generated from the incoming information. One recent study supports an integration of labeled-line and cross-fiber or patterned responses. Using a mouse model and molecular biology techniques, [16] it was found that if a taste receptor cell is changed so that one that normally would be sensitive to sweetness instead expresses a bitter receptor, the animal treats that particular bitter chemical as though it were sweet. This

result indicates that the brain reads the input of certain cells on the tongue as sweet, regardless of how those cells are stimulated. This could be taken as support of the labeled-line hypothesis, since the cells make a one-to-one connection to the brain, or it could be interpreted as support for the cross-fiber or pattern theory, because when the pattern of firing does not change, the perception remains constant even though the stimulus has changed [16].

Although the taste areas of the lower brain are well defined in humans and in mice, the coding of primary tastes by the brain is individualized, especially in cortical areas. There is a pattern of individual brain activity specific to each person, which remains consistent when tested on several different occasions. The amount of variation from person to person is striking [17]. The origins of these idiosyncratic differences in cortical responses to basic tastes are unknown but are almost certainly due to learning and experience as well as genetic influences; however, the study of the origins of these differences is in the early stages. The malleability of the brain response is likely to be influenced by belief and experience. In one study that illustrates this point, the pattern of brain activation to a beverage depended on what people believed that beverage to be rather than what the beverage actually was [18].

3. Sweet and umami

Until recently, there was no consensus about whether umami was a true taste quality at all, much less that it could be categorized together with sweet as we do here. The concept of umami, which perhaps translates best into English as 'savory' or 'meaty,' was suggested by Japanese investigators as a unique quality exemplified by monosodium glutamate (MSG), but with an unusual property of synergy: when MSG is combined with a ribonucleotide, such as inosine monophosphate, the perceived intensity of the mixture is increased above the intensity of either compound alone. Ribonucleotides are a family of compounds often found in meat. Umami was confirmed as a basic taste quality when the umami receptor was discovered (described below). Because part of the umami receptor is shared with a part of the sweet receptor, we discuss these two taste qualities together here.

3.1. Location and receptors

Some people have tongues that are more sensitive to sweetness than others. Investigators who have counted the density of fungiform papillae on the tongue report that the more dense the fungiform papillae, the more intensity of sensation a person perceives from a fixed concentration of sugar [19,20]. Although fungiform papilla number is not a direct measure of taste receptor cell number, since the number of taste buds within a papilla and the number of taste receptor cells within a taste bud are not known, it is reasonable to assume that the number of papillae is positively related to the number of taste receptor cells. The number of fungiform papillae is also correlated with the tongue's sensitivity to touch: people with more fungiform papillae are better able to identify raised letters on a small cube using their tongue than are people with fewer papillae [21]. In more extreme cases, people who have few or no taste papillae due to genetic disorders have reduced or no ability to perceive tastes [22,23]. The balance of the evidence suggests that the number of taste papillae and receptor cells predicts individual intensity ratings to sweet taste stimuli. This relationship applies to bitter perception, as well, where papillae number is related in most studies to bitter sensitivity, e.g., [24], and other references below.

People might differ in number of taste receptor cells, but they might also differ in other ways. For instance, people might vary in the DNA sequence of the sweet receptors or other transduction molecules, with some people having receptors that are better tuned to sweet or umami compounds. Taste receptor cells produce proteins that participate in sweet or umami taste transduction, and some of these proteins are inserted into the cell membrane to form taste receptors. Two proteins combine to create a sweet receptor [25,26]. The names of these proteins

are T1R2 and T1R3, for taste receptor family 1, proteins 2 and 3; the names of the associated genes for these proteins are *TAS1R2* and *TAS1R3*¹ [27]. If T1R3 pairs with the first member of this family, T1R1, the receptor is sensitive to umami compounds.

3.2. Naturally occurring alleles

We assume that genetic variation in sweet or umami receptors can influence taste perception in humans, extrapolating from work in mice and other animals. The taste receptor protein T1R3 was discovered with the aid of mapping experiments in mice, which exploited the differences in sweetness preference of inbred strains [28]. These differences among inbred mice were due to a naturally occurring allele of *Tas1r3* [26,29–34].

Although it is impossible to know exactly what a mouse perceives, there is a chain of evidence that suggests these alleles influence the mouse's perception of sweetness. Alleles of *Tas1r3* correlate with sweetener intake, e.g., [34]. Recordings of the peripheral taste nerves suggest that mice with the low-preference *Tas1r3* alleles exhibit lower nerve firing in response to saccharin or other sweeteners [35,36]. Removal of the functional gene in mice results in a diminished response to most sweeteners [37]. Also, when both genes, *Tas1r2* and *Tas1r3*, are knocked out, the response to sweeteners disappears [38]. Although there are a number of *Tas1r3* alleles that correlate with sweet intake [34], studies of specific DNA variants in cell-based assay systems have identified that exchange of isoleucine to threonine at position 60 of T1R3 as the likely reason for the low saccharin preference in mice [39]. Taken together, these lines of evidence suggest that differences in the DNA sequence of taste receptors can lead to altered taste perception, at least in mice.

Information about the human alleles of the sweet and umami receptor genes is available from public databases. As a part of the human genome project and other projects designed to describe genetic variation, genes have been sequenced in different people and the sequence compared to identify differences among individuals. These differences are assigned a number, currently known as an “rs” number, and are accessible through the primary public data repository of genetic information, the National Center for Biotechnology Information (NCBI). One of the most commonly studied sequence variants are referred to as single nucleotide polymorphisms (SNPs), meaning that one nucleotide has been substituted for another. For instance, in some people, a DNA sequence at a specific location might be ATG, the methionine codon, and in other people it might be ATT, which codes for isoleucine. When nucleotide substitutions lead to differences in amino acid translation they are referred to as non-synonymous or cSNPs. (cSNP is a term related to cDNA, or the coding sequence of DNA.) A summary of cSNPs in umami and sweet receptor genes is given in Table 1.

Some people are specifically insensitive to MSG [40], and although rare, some people appear to be specifically insensitive to sucrose [41]. One explanation for these perceptual differences might be variations in receptor makeup owing to DNA sequence variants in the gene. At this point, there are no genotype–phenotype studies of these polymorphisms in humans, but this is an area of possible research.

3.3. Heterologous expression

Cell-based assay systems have been developed so that proteins can be altered and introduced into cells to study structure–function relationships. These systems are known as heterologous because, in the ideal circumstance, they do not normally contain the foreign proteins of interest. For this reason, native proteins do not interfere with action of the introduced proteins, and

¹TAS1R2 and TAS1R3 are the gene symbols for humans and cats, whereas *Tas1r3* and *Tas1r2* are the corresponding symbols in mice. T1R2 and T1R3 are the symbols for the protein products of these genes.

therefore the interpretation of the results can be based solely on the introduced form of the protein. Heterologous systems have been developed to study the function of sweet receptors. In experiments where the DNA sequence of the genes was modified, the results suggest that small changes in the specific amino acid sequence of the human T1R2 and T1R3 proteins can lead to differences in intracellular signaling in response to sweeteners [42–44].

One of the limitations of heterologous systems is that often a cell type that does not natively express the introduced protein also does not have proteins needed to carry out the new function of the introduced protein. These helper proteins must also be introduced, or the cells must commandeer related proteins already present in the cell to provide those functions. For instance, embryonic human kidney cells can be adapted to function like taste receptor cells by the addition of intracellular signaling molecules and taste receptors [26], but how well the behavior of these cells match the behavior of taste receptor cells in the tongue is not known.

3.4. Modeling

Modeling studies often use information derived from crystallizing a protein with a known amino acid sequence to extrapolate to related proteins with unknown structures. Often modeling studies are done in conjunction with structure–function studies in which a receptor is altered and the predicted outcome based on modeling is compared with the actual outcome of an assay. Usually this is a cell-based assay, but sometimes the allele or changed gene is introduced into an animal, for example, a transgenic mouse. For the sweet and umami receptors, because of the interest in developing new sweeteners, the structure of the sweet receptor was predicted based on the structure of related receptors, and several models have been described (e.g., [31,45]). The sweet receptors follow the structure of class C G-protein-coupled receptors (GPCRs), a type of receptor that weaves in and out of the cell membrane seven times (seven transmembrane domains) and has a long N-terminus. This large piece of the sweet and umami receptors is not very similar to any other protein, and therefore predicting its shape is more difficult. The current model, based on several lines of evidence, is that the dimer of the T1R2 and T1R3 proteins forms a Venus flytrap domain, which provides the ligand-binding pocket. Different sweeteners may bind to either an active or an allosteric site (allosteric sites are those that change the conformation of the receptor in a way that favors increased or decreased signaling but, when bound with ligand, do not directly activate the receptor). Modeling studies are being pursued by multiple laboratories, but thus far differences among people in the receptor gene sequence have not been modeled for their effect on protein function. Once the crystal structures of the sweet and umami receptor complexes are obtained, this information will stimulate work in this area.

3.5. Nerves and brain

One source of variation among people is how much the signal is modified between the taste receptor cell and the afferent nerve fibers. Taste receptor cell depolarization can be modified by hormones, arriving either through the blood stream or because they are secreted by nearby cells. An example of such a hormone is leptin, a hormone that is secreted by fat cells and acts on the brain to suppress food intake and stimulate metabolism. The concentration of leptin in blood varies dramatically among people [46]. In rodents, leptin suppresses the physiological and behavioral responses to sweets [47] and acts on taste receptor cells [48,49]. Although we have no direct evidence to date, it is possible that leptin may affect the function of human taste receptor cells too.

Further upstream, hormones and neurotransmitters that participate in higher-order cortical brain systems that organize the conscious perception of sweet or that regulate the rewarding properties of sweet may affect our reaction to these stimuli, for a review, see [50]. Family studies of addiction have demonstrated that alcoholics and their family members prefer sweeter

solutions than do nonalcoholic family members, suggesting that alcohol and sweeteners may share similar brain reward pathways [51]. The hypothesis that the rewarding properties of opioid-receptor-stimulating drugs and sweet taste are controlled by a common neural substrate is upheld further by the ability of naloxone, an opioid antagonist, to reduce both the positive properties of opiates and the preference for the taste of sweet [52,53]. Scientists are currently investigating alleles of genes that code for opioid receptors to determine if these alleles may be associated with the sensitivity to the rewarding properties of sugar and also to the suppressive abilities of naloxone. The active agent in marijuana increases the hedonic response of rats toward sucrose, which implicates a second system that modifies the pleasure of sweetened foods [54], and it is possible that individual differences would exist in this reward pathway as well.

3.6. Cross-species comparisons

The type of food eaten by a species is one of its defining characteristics. Typically, animal models of human disease are selected in part because either they eat the same foods we do (e.g., primates, mice, and rats) or they respond in a similar way to food. However, animals that differ from us in food intake and taste perception can provide insight into the origin of differences in taste perception and are therefore also a valuable research tool. For instance, both domestic and large cats are predominantly meat eaters and are either indifferent to or avoid sweeteners. Recently, this indifference has been explained by the lack of the sweet receptor gene T1R2, which is broken (a pseudogene) in the domestic cat and in tigers and cheetahs [55]. There is another example of this concept: some species of primates are indifferent to aspartame whereas other species find it sweet. Alleles of T1R2 and T1R3 correlate with this aspartame indifference and may explain the molecular basis of this behavioral observation in primates (Li, personal communication). Genetic differences among members of the same species for sugar responsiveness are common and also occur in fruit flies [56] and honeybees [57]. Taken together, differences in sweet receptors and sweet perception among members of the same species and across species suggest that alleles in these receptors might account for some individual differences in sweet perception among people.

4. Bitter

Although bitter is the opposite of sweet, at least in an everyday sense, and is considered bad and undesirable, bitter perception actually shares several features with sweet perception. The structures of compounds that humans perceive as bitter are diverse, and this is also true of sweet compounds. Both bitter and sweet compounds bind to GPCRs. However, in the case of sweet and umami receptors the family is small, with only three known genes but in the case of bitter receptors the number is large, with perhaps as many as 30 to 50 genes.

4.1. Location and receptors

The family of bitter receptor genes was only recently discovered [58,59]. Multiple bitter receptors are expressed in a taste receptor cell, but bitter receptors and sweet receptors are rarely present in the same cell type. Although the studies we describe below concentrate on this family of receptors, a second path for bitter perception may exist that is independent of the receptors and their G-proteins [60,61]. This second pathway is open to those bitter chemicals that can come into the cell directly (because some bitter compounds are both water and lipid-loving and can permeate into the taste receptor cell). Once inside the cell, the bitter compounds hijack the receptor signaling system, and are responsible for lingering bitter aftertaste [62].

4.2. Naturally occurring alleles

There has been a presumption that naturally occurring alleles of bitter receptors exist because, both in mice and in humans, individual differences in bitter perception are both heritable and specific to some bitter compounds and not others [63–69]. Direct molecular evidence of the existence of naturally occurring alleles was obtained when amino acid substitutions were discovered in one mouse bitter taste receptor that predicted sensitivity to a specific compound [59]. These genetic variants, found in bitter-insensitive mouse strains, also were less responsive in cell-based assays compared with alleles from bitter-sensitive strains. From this study, we learned that alleles of a taste receptor can change both behavioral and cellular responses to bitter compounds.

A second similar discovery was made in humans. Naturally occurring alleles of the *TAS2R38* receptor gene were reported to be responsible for a well-described individual difference in the ability to taste phenylthiocarbamide (PTC) and its chemical relative propylthiouracil (PROP; Fig. 1). Attention to the bitter compound PTC originally came forth when Fox discovered that some people found crystallized PTC to be bitter while others did not [70]. Subsequent studies confirmed this observation and showed that, in most populations, there is a wide distribution of taste thresholds, with a dip in the middle dividing people into tasters and non-tasters, reviewed in [71]. Although this sensory difference among people was well known and well studied, only recently was its genetic basis determined.

The molecular basis of this trait was found through the use of family-based genetic studies. A common form of this type of study compares siblings for a particular trait and determines where in the genome siblings similar in the trait also share common DNA inherited from the parents. This type of study is known as a linkage study, since the shared DNA contains or is near (or linked) to the causal gene. The results of a linkage analysis in human families identified alleles of one member of the bitter gene receptor family, *TAS2R38*, as correlated with PTC sensitivity [72]. Three nucleotide variants (SNPs) in the gene (proline or alanine at position 49, alanine or valine at position 262, and valine or isoleucine at position 296) gave rise to five common haplotypes that accounted for 55% to 85% of the variance in PTC sensitivity. The taster haplotype was defined by the three variants (proline–alanine–valine; PAV) and the non-taster phenotype by the minor alleles (alanine–valine–isoleucine; AVI). A subsequent study of families in a village in Sardinia found similar results: the AVI homozygotes were associated with non-taster phenotype, and heterozygotes and homozygotes of the opposite haplotype were able to taste PTC at low concentrations [73]. There is an additive effect of the haplotype such that people who are heterozygous have lower sensitivities compared with those who are homozygous for the taster form of the receptor, confirming suggestions that homozygotes are especially sensitive to PTC, e.g., [74,75]. When these genetic variants are introduced into cell-based assay systems, the alleles behave as they do in humans: cells with the non-taster form of the receptor do not respond to PTC, whereas cells with the opposite alleles do [76].

Variation in bitter receptor sequence is not confined to the *TAS2R38* locus, and human bitter receptors have more genetic variation within and between populations than do most other genes [77]. One possible explanation is that genes adapt to local conditions, especially to the bitter toxins in food. An implication of this work is that each form of a given bitter receptor might differ in function or maybe even bind different ligands. For instance, although one form of the *TAS2R38* receptor does not respond to PTC, it might respond to other bitter compounds [78]. The role of evolutionary pressure and the current state of the mammalian bitter receptor repertoire and their alleles have been recently reviewed [79]. One provocative hypothesis is the bitter sensitivity coevolved with malaria susceptibility in regions of the world where this disease and bitter plants with quinine-like compounds co-occur [80]. Other investigators have suggested that taste sensitivity and sensitivity to the physiological actions of drugs are related

[81]. Understanding the diversity of bitter response in humans is a growing area of research with implications beyond taste.

4.3. Heterologous expression

Matching the large number of bitter compounds to the appropriate receptors is work that largely lies ahead. To date, two methods for ligand identification have been used: measuring intracellular calcium release in transfected cell lines, and measurement of GTPase binding upon addition of putative ligands to its receptor [59,76,82,83]. The receptor–ligand pairs that have been identified using these methods are summarized in Table 2. For each of these pairs, specificity to each tastant was confirmed by using a variety of bitter compounds. For example, [59] tested cycloheximide, atropine, brucine, denatonium, epicatechin, PTC, PROP, saccharin, an artificial sweetener with a bitter aftertaste, strychnine, and sucrose octaacetate (SOA) for each bitter receptor tested. Of particular value are studies that confirm that the concentration ranges tested on cells correspond to those concentrations that humans can taste [76,82].

4.4. Modeling

The structure of bitter receptors in general can be predicted in the sense that transmembrane sections of the amino acid sequence can be guessed based upon the behavior of similar proteins and the lipophilic versus lipophobic stretches of amino acids. The other structural aspects of the receptors are also being explored; for instance, the taster and non-taster forms of the TAS2R38 bitter receptor differ in their ability to activate the G-protein [84]. As more ligands and receptors are matched, understanding the receptor–ligand interaction in more detail through modeling may become commonplace. Because the bitter receptors do not have a long N-terminus compared with the sweet receptors, molecular modeling is less difficult.

4.5. Nerves and brain

Sweet and bitter transduction follow similar neural pathways, and one potentially interesting area of research is how people with peripheral sensitivity versus insensitivity to a particular bitter compound might differ in brain central processing. For instance, brain images of metabolic activity from people who are PTC tasters might not only differ in taste areas of the brain compared with non-tasters, but also other areas concerned with emotion and hedonics. Likewise, bitter tastes in the mouth might have a different profile of central action if the bitter taste was associated with a drug or reward, such as caffeine or tonic water, compared to bitter tastes without known positive consequences, for example, a food that is unexpectedly bitter.

4.6. Cross-species comparisons

Species differ by log concentrations in their ability to detect bitter compounds [85] and the available evidence would suggest that these differences are partially due to differences in the repertoire of bitter receptor genes [86]. For instance, unlike some humans, mice are not sensitive to the bitterness of PTC but can be made to taste it if the human taster receptor gene is introduced into taste receptor cells [16]. Although it would be logical that animals would have sensitive receptors to the potential toxins in their environment, there appears to be poor agreement between the potency of a poison and its taste threshold [85]. Bitterness may provide information that is broader than whether a compound is poison, it might instead be a signal to “go-slow” and eat only a little bit of something to gauge its effect. For instance, rodents nibble at bitter compounds when ill, presumably testing their effects as medicines, e.g., [87]. Bitter perception may also co-evolve with the ability of a species to eat a plant that is poisonous to others: by doing so, it can carve out a niche for itself and reduces the competition for food. An example of this situation is found among the lemurs—one species is able to eat bamboo that contains concentrations of cyanide that would be fatal to humans and other species of lemurs [88]. It would be interesting to know whether this ability to ingest cyanide is associated with

a loss of taste perception to its bitter properties. Overall, comparisons of species might be one way to uncover a more complex and interesting role for bitter perception beyond poison detection and avoidance.

4.7. Family and twin studies

One way to investigate how differences in the perception of taste qualities are genetically determined is to examine similarity of ratings for intensity and acceptability of different tastants among biologically related people (e.g., parents and their children, twins, or siblings). Heritability refers to a measure of the degree of trait similarity between blood relatives that is due to their shared genetic variation. For most genes and most populations, there is some genetic variation in the DNA that leads to slightly different or sometimes very different protein function (variation in a gene is sometimes referred to as a polymorphism, meaning ‘many bodies’). As an example, genetically identical twins could be exactly the same for a given trait (e.g., eye color), and we would assume that their shared genetic variation (in eye color genes) makes them alike and this variation also makes them different from other people. In the case of another trait, say music preference, genetically identical twins might be as different as any two people chosen at random, and, therefore, we would conclude the music preference is not heritable and is therefore not related to genetic differences. Classic twin designs are particularly useful for heritability estimates in taste research because the degree of taste similarity can be compared between twin pairs that are genetically identical (monozygotic; MZ) and for twin pairs that are no more alike than siblings (dizygotic; DZ). Since each twin pair usually lives together early in life, and is exposed to the same breast milk and the same foods served at home, any differences in taste perception are assumed to be due to genetic differences. For this reason, twin studies are popular research designs used to compute heritability for taste (and other traits that might be influenced by early experiences). However other pairs of family members can also be used for a genetically informative study, as long as the degree of shared genetic variation is known, e.g., parents and children.

While the study of similarity among family members for other sensory systems such as hearing and vision is common, and the resulting work has led to better understanding of their biology, taste has lagged behind these research areas. Little is known about any genetic aspects of taste perception, with the exception of the bitter compound PTC. This compound is easy to measure for its heritable components because differences among individuals are large (some people can taste PTC at low concentrations while others cannot), and polymorphisms in a single gene, *TAS2R38*, have been determined to account for most of the variation among individuals (described above). However, other taste qualities have been more difficult to characterize due to either their polygenic nature or an interaction between genes and the environment. Because of the already complex nature of human taste, we choose to describe here only studies that included laboratory-based psychophysical tests on single tastants or taste qualities (e.g., sweet taste, solutions containing one sweet tastant). We specifically exclude those studies measuring preferences for foods, because food preferences deal in the relationship between taste, smell, texture, and other unique environmental and cultural variables.

One taste quality of particular interest to many researchers in diverse fields ranging from psychology and behavior to nutrition and health is sweet taste perception and its genetic control. Several studies have been conducted in twins and other family members. However, thus far, there is little evidence to support a large heritable component to sweet taste. Krondl et al. [95] investigated the heritability of thresholds for different tastants, including sweet-tasting sucrose by comparing how similar MZ and DZ twins were in their perception of sweetness. While they found a trend that shared genetic variation among twins might account for their similarity, there were too few pairs to be certain of this conclusion. Few other studies have been conducted on the taste intensity or thresholds for the heritability of sweet-tasting solutions.

Several studies have been conducted on sweet preference (as opposed to threshold or intensity measures), and the results of these studies suggest that sweet preferences may be even more complex. One group measured heritability for sweet taste preference between groups of MZ and DZ twins for solutions of sucrose and lactose [89]. However, few differences were found between MZ and DZ twins, and in many cases heritability was not formally calculated because the degree of similarity was higher in the DZ group versus the MZ group of twin pairs. In other words, the more genetically similar twins were more unlike in preference. Other investigators conducted a study on the sweet preferences of DZ and MZ twins, matched for their alcoholic tendencies, by questionnaire and found a small but significant amount of heritability for this trait [90]. However, if alcoholism and sweet preferences are linked through common reward pathways, it is possible those twins selected for common alcoholic tendencies may also share the common genes that contribute to both their desire for alcohol and for sweet taste [51]. If this is the case, this study design could dilute the ability to detect the true heritability of the trait. However, it is also possible that factors within the familial environments of both groups of twins prompted both the heavier use of alcohol and heavier sweet preference. Either hypothesis is plausible, given that the pleasurable qualities of sweet taste and alcohol may share brain pathways and possibly genes in the reward system of the brain.

Additional studies also support the idea that either early experience or genetics may account for sweet taste preferences. A study in a Mexican population measured the liking of differing concentrations of sweetness in a beverage by having people compare their preferred beverages (sweetened coffee) with others of known concentration. Subjects that had been raised on coffees and sweet drinks that were “less sweet” than the “normal” range tended to reject higher sweetness levels [91]. Additionally, a study that measured sweet preferences among young children and mothers in a Brazilian population found a small but significant correlation in preferences for sweet between mothers and children [92]. Another study in mothers and children suggests that differences that are noted in sweet preference between mothers and children may be the function of *TAS2R38* genotype, a bitter gene [93]. A relationship has been found between preferences for sucrose and a genotype that influences bitter perception. Thus, the low but significant correlation between mothers and children seen in this and other studies for sweet preference could possibly result from this or other genes.

Although additional studies are needed to more accurately assess the level of heritability for both the perception and preference for sweet compounds, the literature to date suggests that sweet taste preferences are probably a function of the delicate interaction between factors that exist in the environment in which one lives and the genes that they inherit. However, the specifics of these interactions are largely unknown and require further investigation.

For bitter compounds, including quinine, PROP, and SOA, studies have yielded conflicting findings, particularly for quinine. Smith and Davies [94] measured thresholds for the detection of quinine and found high heritability both between parents and offspring and between groups of MZ and DZ twins [94]. However, two other groups of investigators found no significant heritable component for thresholds of quinine [95,96]. These discrepancies could have been partially influenced by differences in the way heritability was calculated between studies. This problem may be circumvented by new methods for calculating heritability. A recent study used modeling to determine the heritability for thresholds of SOA, PROP, quinine, and caffeine solutions in twins by examining the known differences between twin pairs, using these differences to construct several possible models, and determining the heritability of these solutions using multivariate methods [97]. The results indicated that heritability existed for all four compounds tested, including quinine, but that no common general factor influenced all four compounds. PROP followed a different genetic pathway from that of SOA, quinine, and caffeine. However, heritability was low for SOA, quinine, and caffeine, whereas for PROP (chemically similar to PTC), heritability was higher, perhaps because one gene, *TAS2R38*, can

account for much of the variation in this trait. The results of this study were more consistent with the two studies that found low quinine heritability and differed from the higher levels of heritability noted by Smith and Davies (1973). Overall, the discrepant levels of heritability noted for quinine may be the result of test unreliability or differences among statistical methods for assessing heritability, in other words, the calculated heritability score may wax or wane dependent upon the method used to compute it. Sensitivity to the remaining bitter compounds tested, SOA and caffeine, appears to be moderately heritable. Taken together, these results indicate that perceived intensity of quinine, SOA and caffeine may be complex quantitative traits, without single gene control.

Overall, taste, except in some rare instances, appears to be moderately heritable. However, the genetic and environmental factors that, together, add up to create the quantitative nature of the human taste phenotype make it difficult to assess heritability. Additionally, when heritability is found, it is sometimes difficult to reliably reproduce the result. It is thus clear that more studies, more sophisticated methods to analyze the pathways of possible modes of inheritance, and more ways to reliably test subjects are needed to elucidate the heritability of human taste. Studies where specific genes are assessed for their correlation with specific taste phenotypes (genotype–phenotype correlations) may help provide more clear and specific paths from genes to taste. These studies are reviewed in the next section.

4.8. Genotype–phenotype studies

There is a choice in how to review the scientific literature on PTC sensitivity, the best studied of all are genotype–phenotype correlations for taste-related genes and behavior. On the one hand, the behavioral assays for sensitivity have been in widespread use since the early 1930s, and there are many studies that measure taste sensitivity and make inferences about the genotype, e.g., [98]. However, there are far fewer studies that measure genotype, since the underlying gene and its alleles were only recently discovered. Since psychophysical results are sensitive to method [99], and the methods used to assess bitter sensitivity vary considerably, in this section we consider only studies that assessed genotype directly, that is, through genotyping of DNA. The interested reader is referred to previous reviews of studies that measured PTC or PROP sensitivity and taste or other food-related behaviors [98,100–103]. This section necessarily focuses on the *TAS2R38* gene since few other phenotype–genotype relationships between human taste receptor genes and behavior have been described.

Thus far, three studies have examined phenotype–genotype relationships among bitter receptor genes and some aspect of human behavior (beyond perception of the bitter ligand). The first such report focused on alcohol drinking; in this study, 84 healthy adults were assessed for *TAS2R38* genotype and alcohol intake, and the investigators report that the non-taster genotype was a significant predictor of alcohol consumption [104]. A second study focused on children and their mothers and demonstrated that children with the non-taster *TAS2R38* genotype had lower sucrose preferences than children with taster alleles [93]. In a third report, a cross-sectional study of older British women, none of the *TAS2R38* genotypes were associated with dietary intake as measured by a food frequency questionnaire, but the non-taster genotype was a predictor of diabetes [105]. Another bitter receptor, involved in salicin perception [82], is related to human alcohol intake [106]. It is curious that the initial studies of two bitter receptors and their alleles have reported a relationship to alcohol consumption; why this is so is not clear. It is also curious that for PTC, the non-taster allele is associated with higher alcohol intake (among people who are not problem drinkers) but the non-taster allele is associated with lower sweet preference, at least in children. This observation is inconsistent with the greater sweet preference in alcoholics [51]. Taste could be a more important regulator of alcohol consumption than previously appreciated [107], but the interactions among sweet liking, alcohol

consumption and taste will no doubt be more complex than a simple one-to-one correspondence between genotype and behavior.

5. Taste perception and behavior, health and nutrition

Taste perception and the human response to bitter and sweet chemicals may have a wide-ranging effect on health and nutrition, and genetic differences among people may account for health outcomes in the population. Bitter compounds at high concentrations generally elicit food rejection, a behavior critical to avoid ingesting the many toxic compounds found in foods, such as rancid fat, hydrolyzed protein, and plant alkaloids [108]. Although many bitter foods are harmful and should be avoided, there are bitter compounds in fruits and vegetables with beneficial effects on health [109–111]. Some of these compounds include phenols (found in tea, citrus fruits, wine, soy), triterpenes (citrus fruits), and organosulfur compounds (cruciferous vegetables, e.g., broccoli and cabbage). Public health efforts to increase fruit and vegetable intake have been challenging, and the resistance to increase consumption may in part be due to the bitter tastes of these foods. Indeed, many of the “healthy” vegetables such as cruciferous vegetables are often disliked, especially by children [112], perhaps for their bitter taste [101,113,114].

Variability in bitter taste perception may influence the risk, perhaps for their bitter taste of diet-related conditions such as heart disease, obesity, and cancer, e.g., [114,115]. However these relationships have not been found consistently, perhaps because the connection between the PTC taste polymorphism and food is not direct. PTC itself is not found in foods, but chemically related compounds are, mostly in vegetables such as cabbage and turnips [116]. Because people that can or cannot taste PTC are found in almost all human populations, this might be taken as evidence that this polymorphism has been subject to ‘balancing selection’, or a selection for heterozygous individuals in the population [79,117,118]. Under balancing selection, both alleles are maintained in the population because they are useful. In the case of PTC, for instance, perhaps non-tasters may be less prone to reject healthy bitter foods and may choose a diet with more variety, whereas tasters might be less likely to eat foods that might poison them.

While the connection between bitter receptor alleles and bitter perception is well described in humans, at least in the case of one member of the bitter receptor family, no direct connections have been described for sweet receptors and sweet perception in humans. Although there are individual differences in the human psychophysical responses to sweeteners [119,120,121], and some evidence indicates that sweet perception is somewhat heritable (described above), the differences among people are not as large as they are for bitter perception. However since DNA sequence variants have an effect on the intake of sweeteners in mice and cats, it is at least possible that this is also true in humans.

The methods described above had examined the taste–genotype connection by identifying genes that participate in taste perception and measuring how variation in these genes translate into differences among people in their sense of taste. This approach does not address how individuals might vary in food selection and whether genetic variation has a role to play. Progress is being made in this area however through the use of genetic methods. In one type of study, family members are compared for their pattern of food intake and also for their sharing of genomic regions across all chromosomes. Two studies have reported that sugar intake is linked to several chromosomal locations [122,123], one of which is near a sweet receptor gene (*Ip36*). If the genetic variation important in the determination of food habits can be described, we can then assess the relative contribution of the taste genes to overall food intake. Since many public health problems such as obesity are currently attributed to poor diet, understanding the genetic basis of eating, for instance, high-sugar foods is of immediate concern.

Most geneticists agree on one simple principle of their discipline: that which is inherited by organisms from their forebears is a choice of capabilities to respond to a range of environments [124]. Because humans occupy almost all habitats on the earth, eating the plant and animal food available, it is not surprising that the inherited ability to taste is as wide-ranging as the human diet. At the molecular level, the connection between genetic variation and person-to-person variation in taste perception has been established for at least some bitter stimuli, and with these proven genetic methods at hand, we anticipate that, looking forward, the connection between taste perception, genetic variation, and food intake will be explored with vigor. One might imagine that consumer food products will be tailored to accommodate differences in genotype-based tasting ability. In a sense, humans do this already by cooking and producing foods with different spices or added sugars and salt, but genotype information introduces a biological and perhaps more rational approach to cater to different tastes. We also anticipate that genetic testing might be performed at birth to identify in advance those most likely to reject bitter vegetables or to embrace highly sweetened foods. How information about how taste genotype might be used, in practice, in a principled and ethical way, to better human health and diet remains to be seen.

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Phenylthiocarbamide (PTC)   **Propylthiouracil (PROP)**

Fig. 1.
Chemical structures of PTC and PROP.

Table 1

Summary of alleles of the human sweet and umami receptors available from public sources

Gene	Identifier	Allele
<i>TAS1R1</i>	rs10864628	E347K
<i>TAS1R2</i>	rs9701796	S9C
<i>TAS1R2</i>	rs28374389	V486I
<i>TAS1R2</i>	rs6662276	A574T
<i>TAS1R2</i>	rs9988418	K838R
<i>TAS1R3</i>	rs307377	C751R
<i>TAS1R3</i>	rs12030791	V810L
<i>TAS1R3</i>	rs12030797	F817L
<i>TAS1R3</i>	rs188647	G877A
<i>TAS1R3</i>	rs307374	L887F

Genes symbols for the sweet and umami receptor genes are given in the first column. Note that 'TAS' in the gene symbol refers to taste and that the number 1 indicates that these genes are from the first family described. The letter R denotes a receptor, and the genes are given a final number to show the order of discovery. The identifier is listed with an rs number, which is a publicly available unique identifier assigned and administered through the NCBI database. Alleles are shown only for nucleotide changes that result in a predicted change in amino acid translation (i.e., nonsynonymous changes). The numbers refer to the amino acid changed; e.g., for the *TAS1R1* allele E347K, glutamine is substituted with lysine at amino acid position 347. The accession numbers of the genes are NM_138697 (*TAS1R1*), NM_152232 (*TAS1R2*), and XM_371210 (*TAS1R3*).

Table 2

Taste receptors and their known ligands

Species	T2R	Ligand	Detection system	Reference
Mouse	mTAS2R5	Cyclohexamide	Ca ²⁺ release, GTPγS binding	[59]
	mTAS2R8	Denatonium, PROP	Ca ²⁺ release	[59]
Rat	rTAS2R9	Cyclohexamide	Ca ²⁺ release	[82]
Human	hTAS2R4	Denatonium, PROP	Ca ²⁺ release	[59]
	hTAS2R10	Strychnine	Ca ²⁺ release	[82]
	hTAS2R14	Broadly tuned	Ca ²⁺ release	[125]
	hTAS2R16	Salicin	Ca ²⁺ release	[82]
	hTAS2R44	6-Nitro-saccharin, denatonium	GTPγS binding	[83]
	hTAS2R61	6-Nitro-saccharin	GTPγS binding	[83]
	hTAS2R38	PTC, PROP	Ca ²⁺ release	[76]
	hTAS2R43	Aristolochic acid, saccharin, acesulfame K	Ca ²⁺ release	[126]
	hTAS2R44	Aristolochic acid, saccharin, acesulfame K	Ca ²⁺ release	[126]

In some cases where large chemical families were tested and found to stimulate the receptor, the exemplar compound for the family is listed.