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Genetics of sweet taste preferences†

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ABSTRACT: Sweet taste is a powerful factor influencing food acceptance. There is considerable variation in sweet taste perception and preferences within and among species. Although learning and homeostatic mechanisms contribute to this variation in sweet taste, much of it is genetically determined. Recent studies have shown that variation in the T1R genes contributes to within- and between-species differences in sweet taste. In addition, our ongoing studies using the mouse model demonstrate that a significant portion of variation in sweetener preferences depends on genes that are not involved in peripheral taste processing. These genes are likely involved in central mechanisms of sweet taste processing, reward and/or motivation. Genetic variation in sweet taste not only influences food choice and intake, but is also associated with proclivity to drink alcohol. Both peripheral and central mechanisms of sweet taste underlie correlation between sweet-liking and alcohol consumption in animal models and humans. All these data illustrate complex genetics of sweet taste preferences and its impact on human nutrition and health. Identification of genes responsible for within- and between-species variation in sweet taste can provide tools to better control food acceptance in humans and other animals. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: sweet; taste; behaviour; genetics; receptor

Introduction

Sweet Taste

The sense of taste has probably evolved to allow animals to choose and consume appropriate food. The most common natural taste stimuli that humans describe as sweet are sugars. Sugars are important nutrients for animals from many different species ranging from insects to mammals. In animals from many species, sugars are recognized by the taste system and evoke appetitive consummatory responses.[1] In addition to sugars, a wide range of other chemicals (referred to here as sweeteners), also evoke the sensation of sweetness in humans and are palatable to many other animals. Numerous studies have shown that the mechanisms of taste perception of sweeteners are similar in humans and non-human mammals. This justifies using laboratory animals, such as mice and rats, as model organisms to study mechanisms of sweet (sucrose-like) taste relevant to humans.

In addition to evoking behavioural responses, sweet taste stimuli can elicit preabsorptive cephalic phase responses, such as insulin release,[2–4] activate endogenous opioidergic, dopaminergic and serotonergic systems[5–12] and produce analgesic effects in children and young animals.[13–17] Taste responses to sweeteners are modulated by post-ingestive feedback and hormones.[18–24] Because ingested sugars evoke sweet taste sensation and also produce rewarding post-ingestive feedback,[25–27] sweet taste preferences can be modified by the experience of consuming sugar. These effects of experience are strong enough to alter initial genetic differences in sweet taste responsiveness.[28–30] Although appetitive responses to sweet taste stimuli are inborn in many animals,[31,32] they are also often modulated by environment and depend on genetic factors.[33,34] The interactive mechanisms of sweet taste suggest that it is a part of a complex ingestive behaviour and is likely to be determined by multiple genes.

Sweet Taste Receptors

In mammals, sweetness perception is initiated when sweeteners interact with taste receptor proteins from the T1R family expressed in taste receptor cells in taste buds of the oral cavity. Thus, sweeteners function as ligands of the G protein coupled T1R receptors. The mammalian T1R gene family consists of three genes named 'taste receptor, type 1, member 1, 2 or 3'. Corresponding gene symbols abbreviate these names to *TAS1R1*, *TAS1R2* or *TAS1R3* (in humans) or *Tas1r1*, *Tas1r2* or *Tas1r3* (in rodents and other non-human animals). Corresponding protein symbols are T1R1, T1R2 and T1R3. Species origin of a protein can be indicated as hT1R1 (human T1R1) or mT1R1 (mouse T1R1). For brevity, when we refer to both human (*TAS1R*) and non-human (*Tas1r*) genes, we describe

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them as T1R genes. The three mouse *Tas1r* genes are located in the distal chromosome 4 in the order: *Tas1r2 – Tas1r1 – Tas1r3*. Their human orthologues reside in a region of conserved synteny in the short arm of human chromosome 1 (1p36) in the same order: *TAS1R2 – TAS1R1 – TAS1R3*. The mouse *Tas1r* genes contain six coding exons that are translated into 842–858 amino acid proteins. 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 (VFT) domain and a cysteine-rich domain connected to the heptahelical domain.

There is strong evidence that T1R2 and T1R3 proteins function as sweet taste receptors. Although T1R genes are expressed in several different internal organs (reviewed by Bachmanov and Beauchamp[35]), their main sites of expression are taste receptor cells of the taste buds. In mice and rats, T1R2 and T1R3 are co-expressed in the same taste cells, but some taste cells express only T1R3.[36–38] Co-expression of T1R2 and T1R3 in the same taste cells suggested that they may function as heterodimers, which is believed to commonly occur with GPCRs.[39] Consistent with this, cells heterologously expressing both T1R2 and T1R3 respond to sweeteners,[38,40,41] but T1R3 may also function as a low-affinity sugar receptor alone, probably as a homodimer.[42] Finally, genetically engineered mice with targeted mutations of the *Tas1r2* or *Tas1r3* genes have diminished taste responses to sweeteners.[42,43]

There is also evidence that sweet taste reception may be not limited only to the T1R-mediated mechanisms. Glucose transporter 4 (GLUT4), sodium–glucose co-transporter (SGLT1), and ATP-gated K^+ (KATP) metabolic sensors are present in T1R3-expressing taste cells and may serve as mediators of the T1R-independent sweet taste of sugars in mice.[44] In addition, some sweet-tasting compounds can penetrate the TRC membrane and act on intracellular targets,[45] which in this case could function as intracellular receptors of such compounds.

Behavioural Genetics of Taste

In genetic terms, measurements of the sweet taste preference are considered phenotypes, or traits. Phenotype is defined as the observable characteristics of an organism determined by both genetic make-up and environmental influences. The goal of the genetic analysis is to separate the genetic and environmental effects on phenotype.

In humans, taste phenotypes are usually rating sensation intensity on a scale with verbal descriptors or by reporting a perceptual difference between samples. These techniques allow one to evaluate sensitivity, intensity, quality and hedonic value of the taste sensation. Human sweet taste preference and liking can also be evaluated by measuring consumption or cravings of sweet foods using questionnaires or records of intake.

Studies of model organisms help to understand the genetic mechanisms of variation in sweet taste preferences. Laboratory animals offer an important advantage in these studies because inbred strains are available for several species. Animals within an inbred strain are genetically homogeneous. Therefore, the within-strain variation is due to non-genetic (environmental) factors, but differences between strains represent genetic variation.

Assessment of taste perception in non-human animals relies on a number of different techniques to record behaviour elicited by taste stimuli.[46] These techniques include two-bottle preference tests, brief-access lick recording tests, and approaches that require animal conditioning to examine generalization and discrimination between taste stimuli, and to measure taste thresholds.

Many taste phenotypes are measured using a continuous quantitative scale (e.g. volume of solution consumed, preference score or lick rate) and thus are considered quantitative traits. Genes with allelic variants that underlie variation of quantitative traits reside in chromosomal regions named quantitative trait loci (QTL). Defining these chromosomal regions through genetic linkage analysis is called QTL mapping. QTL mapping helps to identify DNA sequences of genes in the QTL regions and to find genes that are responsible for phenotypical variation. Because this approach to identify genes is based on a chromosomal position of a phenotypical locus, it is called positional cloning. Quantitative traits that depend on multiple genetic and environmental factors are considered complex traits. There is strong evidence that sweet taste preference is a complex trait.

Species Differences in Sweet Taste Preferences

Although many vertebrate and invertebrate animals detect taste of sugars and avidly consume them, receptors for sugars evolved independently in these two lineages. The vertebrate T1R receptors are not found in invertebrates[47] and are not related to a Drosophila taste receptor for a sugar trehalose encoded by the *Gr5a* gene.[48–53] Numbers of the T1R genes in different vertebrate species range from complete absence in the frog to five in some fishes.[40,47,54–63] Ligands for the T1R receptors have been experimentally confirmed only for a few species (mostly humans and rodents), but it is likely that their orthologues in other species have similar ligand specificities. Therefore, species differences in sweet taste preferences could be due to variation in the T1R genes.

There are several examples of differences in sweet taste preferences among species of vertebrate animals. Despite nearly universal preference for sugars, the chicken and Felidae species (domestic cat, tiger, lion and cheetah) are not attracted to sugars and other sweeteners.[64–69] Mammals also differ in preferences for artificial sweeteners, for example aspartame.[70,71] Species variation in the T1R receptors plays prominent role in these differences in sweet taste preferences.

Sweet Taste Blindness in Cats and Other Species

Domestic cats (*Felis silvestris catus*) and their wild relatives from the family Felidae are obligate carnivores. They do not show preferences for sweeteners, but otherwise have the normal sense of taste.[64,65,69] We have identified the cat *Tas1r2* and *Tas1r3* genes.[56] The cat *Tas1r3* gene shows high sequence similarity with functional *Tas1r3* genes of other species and is expressed in taste buds. However, the cat *Tas1r2* is a pseudogene (Figure 1) with no evidence of its expression. The *Tas1r2* genes of three other Felidae species, the tiger (*Panthera tigris*), cheetah (*Acinonyx jubatus*) and Asiatic lion (*Panthera leo persica*), are also pseudogenes.[56,69] Because cat *Tas1r2* is an unexpressed pseudogene, a functional sweet taste receptor heteromer T1R2+3 cannot form, which explains the molecular origins of sweet taste blindness in cats.

Tas1r2 pseudogenization and lack of sweet taste responsiveness in cats are probably results of these animals being obligate carnivores that do not seek sugars in their food, and thus do not have a selective advantage of having a functional sweet taste

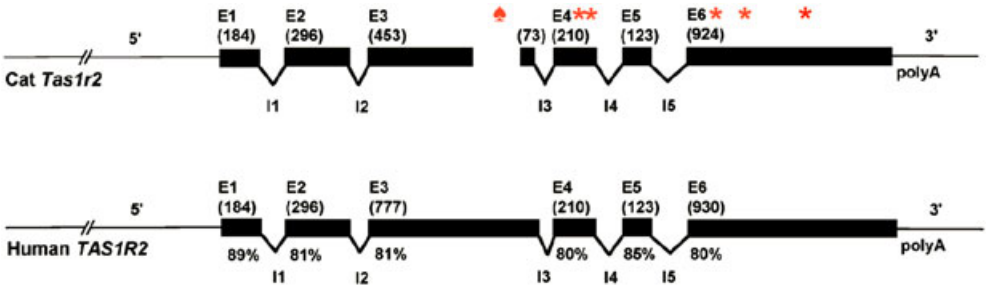

Figure 1. Structures of the cat *Tas1r2* and human *TAS1R2* genes. The cat *Tas1r2* gene has a 247-base pair micro-deletion (♠) in exon 3 and stop codons (*) in exons 4 and 6. The exons are shown as black bars; exon numbers and size (bp; shown in parentheses) are indicated above the bars. The % similarity between corresponding human and cat exons at the nucleotide level are indicated under the human exons. Introns are not scaled proportionally because of their large size. Reproduced from Li *et al.*[56] with open-access licence from the Public Library of Science (PLoS)

receptor that recognizes sugars. Other species of the order of Carnivora (dogs, *Canis lupus familiaris*, Canidae family; lesser panda, *Ailurus fulgens*, Ailurus; domestic ferret, *Mustela putorious furo*, Mustelidae; Haussa genet, *Genetta thierry*, Viverridae; meerkat, *Suricata suricatta*, Herpestidae; and yellow mongoose, *Cynictis penicillata*, Herpestidae) have a functional *Tas1r2* structure[56,57,69] and are attracted to sugars.[69,72,73] Thus, *Tas1r2* pseudogenization was an important event in the evolution of the cat's carnivorous behaviour.

Similarly to cats, chickens also lack functional *Tas1r2* gene.[57,61] Interestingly, some other birds recognize sugar taste,[74,75] suggesting that they may have a functional T1R2. Thus, pseudogenization of *Tas1r2* occurred multiple times in evolution. Loss of *Tas1r2* in cats and chickens may be a consequence of their feeding behaviour that does not require a sweet taste receptor for proper food choice. However, a reverse causative relationship is also possible, when a loss-of-function mutation in the *Tas1r2* gene resulted in loss of sweet taste sensation, which in turn altered feeding behaviour of these animals.

The role of pseudogenization of T1R genes in evolution of feeding behaviour is also illustrated, by a recent finding that *Tas1r1* is a pseudogene in the giant panda (*Ailuropoda melanoleuca*),[76,77] which deems its umami/amino acid taste receptor dimer T1R1+3 non-functional. Most species of the order Carnivora have an intact *Tas1r1*. The giant panda also belongs to the order Carnivora, but it eats almost exclusively bamboo, and estimated time of its dietary switch to bamboo coincides with time of its *Tas1r1* pseudogenization.[76]

Perception of Aspartame Sweetness in Primates and Other Species

Aspartame is a commercially available low-calorie sweetener widely used in foods and beverages. Aspartame preference and the ability to taste aspartame sweetness vary among mammalian species. Humans, apes and Old World monkeys perceive aspartame as sweet, but other primate species, and most of non-primate species, do not. We analysed the association of aspartame taster/non-taster status and sequence variants of the sweet taste receptor proteins, T1R2 and T1R3, in several species. Nine variant sites in T1R2 and 32 variant sites in T1R3 distinguished aspartame tasters and non-tasters. We next examined whether any of these variant sites disrupt interaction between aspartame and the T1R2+3 receptor. Molecular docking of aspartame to computer-generated models of the T1R2 + T1R3 receptor dimer identified primary active binding sites in the VFT domain of the T1R2 and T1R3 proteins. In addition, previously unknown allosteric sites were identified. Sequence variants at the T1R2 allosteric binding site (Figure 2) likely influence the interaction of aspartame with the primary binding site and ability of aspartame to activate the receptor, and therefore an animals' ability to taste sweetness of aspartame.[78]

Within-species Variation in Sweet Taste Preferences

Humans

Humans differ in their perception of sweet taste.[79–86] One of the best known examples of this variation is a sweet liking phenotype (Figure 3): in 'sweet-likers', hedonic ratings of sucrose solutions monotonously increase with increasing concentrations, while in 'sweet-dislikers' at higher sucrose concentrations the ratings decrease.[81,86] Mechanisms underlying human variation in sweet taste, including 'sweet-liker' and 'sweet-disliker' phenotype could be complex: they may involve peripheral or central taste processing and can be genetically determined, acquired or depend on interaction between genetic and environmental factors. Nevertheless, genetic factors explain at least part of variation in sweet taste preferences in humans.[33,34,87–94]

T1R-dependent variation

In humans of African, Asian, European and Native American origin, all three *TAS1R* genes have multiple polymorphisms, which include those resulting in amino acid changes of the T1R proteins. The majority of amino acid sequence variation occurs in the N-terminus extracellular domain, where taste ligands are likely to bind to the taste receptors. *TAS1R2* is particularly diverse compared with other human genes: its rate of polymorphisms is in the top 5–10% of all human genes surveyed. The high rate of *TAS1R2* variation was predicted to result in variation in sweet taste perception.[95] This prediction was confirmed in a recent study, which demonstrated association of Ile191Val variant in *TAS1R2* with habitual consumption of sugars in overweight and obese individuals.[96]

Another recent study has shown that non-amino acid coding single nucleotide polymorphisms (SNPs) in the *TAS1R3* promoter are associated with taste sensitivity to sucrose in humans. These polymorphisms influenced promoter activity in an *in vitro* luciferase reporter assay, which indicates that they affect *TAS1R3* gene transcription.[97]

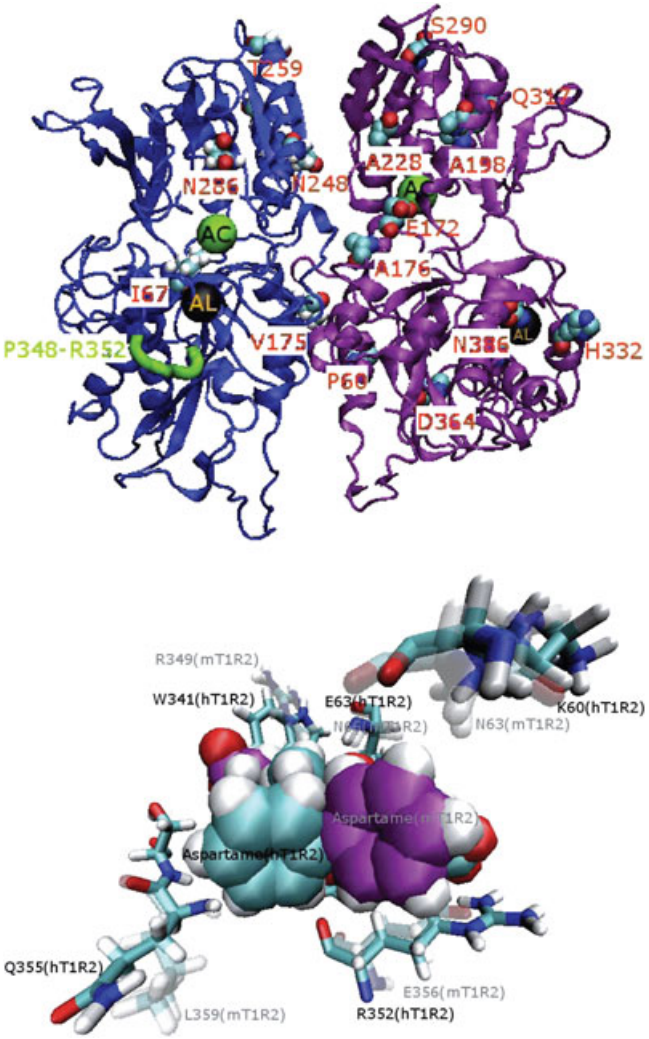

Figure 2. Sequence variants predicted to influence interaction of the T1R2+3 receptor with aspartame. Top panel: VFT domain of the hT1R2 (active–close)-hT1R3 (active–open) heterodimer. The C-alpha trace for hT1R2 is shown as blue ribbon; hT1R3 is shown in purple. Centres of binding regions are shown as green or black spheres. The green spheres (labelled AC) indicate binding regions at the centres of the VFT domains referred to as active sites. Black spheres (labelled AL) indicate binding regions referred to as allosteric sites. Taster/non-taster variant sites are shown as space-filled representation. The hT1R2 segment P348–R352 (PPLSR; shown in green ribbon) is a part of the allosteric site. It is deleted in most aspartame non-tasters and is replaced with PMPNE in the mouse. This segment is important for the spatial arrangement of the putative allosteric site (see bottom panel). Bottom panel: Aspartame (carbon atoms are cyan) bound to the allosteric site of hT1R2 is superposed to aspartame (carbon atoms are purple) bound to the allosteric site of mT1R2. Amino acids within 4.5 Å of bound aspartame in hT1R2 are shown in stick representation (the equivalent amino acids in mT1R2 are shown as shadows). R352 (a part of a polymorphic segment P348–R352) in hT1R2 is predicted to be directly involved in binding of aspartame to the putative allosteric site. Substitution of R352 in hT1R2 with a corresponding residue, E356, in mT1R2 changes orientation of aspartame within the allosteric site and leads to stronger binding of aspartame to the mouse site compared with the human site. This likely interferes with aspartame binding to the active site of mT1R2+3 and prevents receptor activation. Reproduced from Li *et al.*[78] by permission of the Oxford University Press

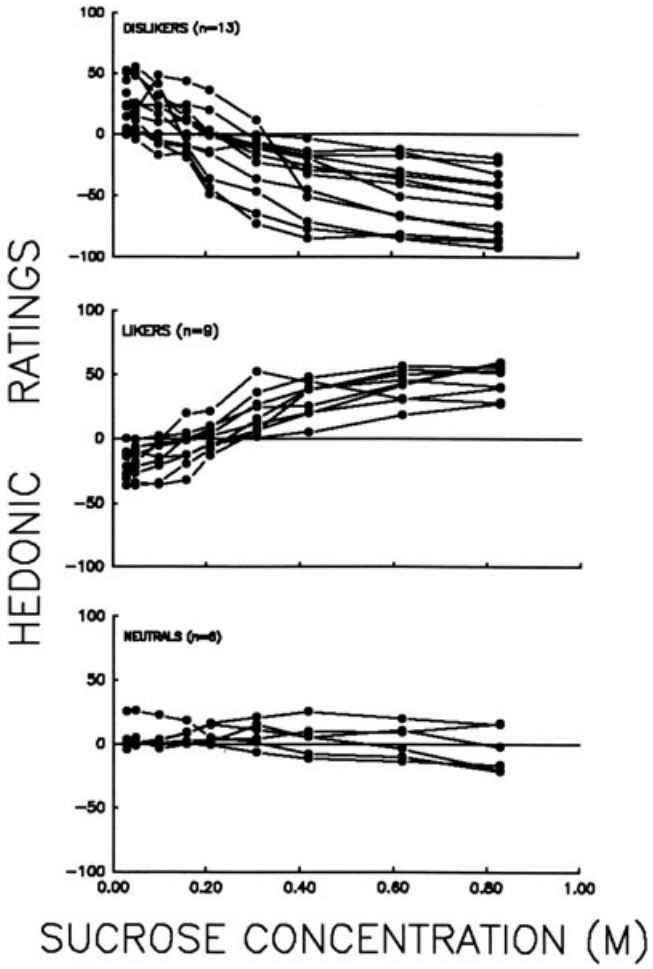

Figure 3. The variation in sweet-liking in humans: individual hedonic ratings of sucrose. 'Dislikers' report a general decrease in pleasantness as concentration increases, 'likers' report an increase in pleasantness with increasing concentration, and 'neutrals' have a minimal affective response to all concentrations of sucrose. Reproduced from Looy and Weingarten[86] by permission of the Oxford University Press

T1R-independent variation

Genetic factors responsible for variation in human sweet taste preferences are not limited to polymorphisms of the sweet taste T1R2+3 receptor. While human *TAS1R2* or *TAS1R3* genes reside in chromosome 1, a genome-wide linkage study has detected a QTL for use frequency of sweet foods on chromosome 16.[94] Candidate gene association studies indicate that T1R-independent genetic variation in sweet taste preferences involves both peripheral and central mechanisms. The *GNAT3* gene encodes the taste-specific Gα protein subunit gustducin expressed in taste bud cells in the tongue. Several SNPs in the non-coding regions of *GNAT3* (upstream of the ATG translation start site and within introns) are associated with human sucrose perception.[98] The dopamine D2 receptor (*DRD2*) is involved in the rewarding effects of sugar. Glucose transporter type 2 (*GLUT2*) was suggested to function as a glucose sensor in the brain and to be involved in regulation of food intake. Amino acid coding

variants in both of these brain-expressed genes, *DRD2* and *GLUT2*, are associated with habitual consumption of sugars by humans.[99,100]

Mice

Prominent genetic differences in taste responses to sweeteners among inbred strains of mice were shown using different experimental techniques and a variety of sweeteners (e.g. sucrose, glucose, dulcin, saccharin, acesulfame, glycine, D-phenylalanine and L-glutamine). Mice from different strains differ in taste responses to sweeteners assessed using long-term preference tests,[101–113] single-bottle tests,[114] brief-access tests based on lick recording,[115] taste detection thresholds,[116] conditioned taste aversion generalization,[117] and responses of gustatory nerves.[118–120] These studies have shown that responses to many of these sweeteners (e.g. sucrose, glucose, dulcin, saccharin and acesulfame) closely correlate among mouse strains, suggesting a common genetic basis for sweet taste. However, responses to some sweet-tasting amino acids display somewhat different patterns of strain differences.[121]

Some genetic analyses of sweetener consumption by mice yielded evidence that it is influenced by a single locus, named *Sac* (saccharin preference),[102,106,110,122] whereas other experiments indicated that more than one gene is involved.[107,110,111,123,124] The apparent discrepancy in whether the single-gene or the multi-gene model better describes genetic variation in sweetener preferences is likely due to use of different progenitor strains and types of mapping panels, different sweetener solutions tested, and different quantitative analyses used in these studies.

T1R-dependent variation

Genetic analyses and positional cloning of the *Sac* locus were instrumental in discovery of the T1R sweet taste receptor genes. Studies using crosses between different inbred mouse strains have mapped the *Sac* locus to the subtelomeric region of mouse chromosome 4[110,123,125,126] and have shown that it affects sweetener preferences[102,106,110,122,123,125,126] and the afferent responses of gustatory nerves to sweeteners.[126,127] Our positional cloning study has shown that the *Sac* locus corresponds to the *Tas1r3* gene[60,113,128] and that *Tas1r3* sequence variants are associated with sweetener preference phenotypes in genealogically diverse mouse strains.[60,113] Additional evidence for identity of Sac and *Tas1r3* was obtained in studies using congenic,[60] transgenic[38] and knockout mice.[42,43] Furthermore, allelic variants that confer different sweet taste responsiveness in mice also influenced receptor properties in *in vitro* assays.[41,129] We analysed association of the *Tas1r3* sequence variants with saccharin preferences in a large panel of genealogically diverse inbred mouse strains.[113] This analysis has identified an amino acid substitution of isoleucine to threonine at position 60 (I60T) as a candidate causative variant for phenotypical variation in sweet taste preferences. Because this sequence variant is in the extracellular N-terminus of the predicted T1R3 protein, we proposed that it affects ligand binding.[113] This prediction was subsequently confirmed in an in vitro study showing that a corresponding site-directed mutation changes binding affinity of the T1R3 protein to several sweeteners.[129]

Allelic variation of the *Tas1r3* gene influenced taste responsiveness to non-nutritive sweeteners (saccharin, acesulfame-K, sucralose, SC-45647), sugars (sucrose, maltose, glucose, fructose), sugar alcohols (erythritol, sorbitol), and some amino acids (D-tryptophan, D-phenylalanine, L-proline). *Tas1r3* genotype did not affect taste responses to several sweet-tasting amino acids (L-glutamine, L-threonine, L-alanine, glycine), glucose polymers (Polycose, maltooligosaccharide), and non-sweet NaCl, KCl, citric acid, HCl, quinine, monosodium glutamate, ammonium glutamate, and inosine 5′-monophosphate. Thus, *Tas1r3* polymorphisms affect taste responses to many nutritive and non-nutritive sweeteners (all of which must interact with a taste receptor involving T1R3), but not to all carbohydrates and amino acids.[130,131]

T1R-independent variation

Several studies have shown multigenic inheritance of sweetener preferences.[107,110,111,123,124] Consistent with these findings, several lines of evidence indicate that allelic variation of the mouse *Tas1r3* locus does not account for all the genetically determined differences in sweetener preferences. Analysis of multiple inbred mouse strains has shown that the *Tas1r3* genotype explains only 78% of genetic variation in saccharin preference.[113] In the B6 × 129 F2 cross, the *Tas1r3* genotype explained 64–96% of genetic variation in preference scores for different sweeteners, but only 10–35% of genetic variation in sweetener intakes.[126,130] Responses to sweeteners in brief-access tests differ among mouse strains but do not seem to be associated with *Tas1r3* alleles.[115] Thus, a substantial part of the genetic variation in taste responses to sweeteners among mouse strains is attributed to loci other than *Tas1r3*. Taste responses to glycine provide a remarkable example: although mouse strains differ in responses to glycine,[110,132] this variation is not attributed to the *Tas1r3* genotypes.[116,130]

One of the genetic loci affecting sweet taste responses is *dpa* (D-phenylalanine aversion), which affects ability of mice to generalize conditioned taste aversion between D-phenylalanine and sucrose, inferring that *dpa* affects ability to detect the sweetness of D-phenylalanine. The *dpa* locus also affects responses of sucrose-sensitive fibres of the chorda tympani nerve to D-phenylalanine. The *dpa* locus was mapped to proximal chromosome 4, a region distinct from the subtelomeric chromosome 4 harboring the *Tas1r* genes.[133–136] It was suggested that the *dpa* locus can also affect responses to sweeteners in two-bottle tests.[111] Consistent with this, a locus on proximal chromosome 4, in the *dpa* region, was found to be suggestively linked to consumption of, and chorda tympani responses to, sucrose.[126] An epistatic interaction between effects on sucrose intake of this locus and the *Tas1r3* locus suggests that these two loci may encode interacting components of sweet taste transduction.[126]

To study the non-*Tas1r* genes involved in sweet taste, we began selective breeding of mouse lines divergent in sweetener consumption. To eliminate the *Tas1r3* effects, we crossed B6 inbred mice with 129.B6–*Tas1r3* congenic mice. As a result, all mice in this cross had only the B6 *Tas1r3* allele. Despite genetic identity at the *Tas1r3* locus, mice from the F2 generation varied widely in consumption of 20 mM saccharin and 30 mM glycine, but there was no correlation between these two traits. We therefore began selective breeding of mouse lines with high and low saccharin intakes, and with high and low glycine preferences.[55,137] The large divergence between the selected strains demonstrates that much of genetic variation in mouse

sweet taste responses depends on genes other than *Tas1r3*. To map these genes, we genotyped mice from the selected strains and found linkages on four chromosomes in mice selected for glycine preference, and linkages on five chromosomes for mice selected for saccharin intake. We have found the complex genetic architecture of sweetener preferences, with each progenitor strain contributing loci increasing or decreasing a trait value, and with two distinct sets of genes for glycine and saccharin consumption.[138–140] Consistent with our genetic mapping studies, mice with mutations in genes other than taste receptors also have altered behavioural responses to sweeteners.[141–145] Furthermore, taste responses to complex carbohydrates (malto oligosaccharide and Polycose) are not affected by allelic variants of the *Tas1r3* gene.[131,146,147]

Other Species

Although most research on genetics of sweet taste was conducted in mice, strain differences in sweetener preferences have been reported for rats[148–152] and hamsters.[153] Rat T1R3 is a part of the taste receptor responding to saccharin.[38,40,154] However, rat strains with different saccharin preferences do not differ in protein sequence of T1R3.[155] Consistent with this, QTLs for saccharin preference in the rat were mapped to chromosomes 3, 16 and 18, but not to chromosome 5 where rat *Tas1r3* resides.[156] Therefore, rat strain differences in saccharin preferences depend on genes other than *Tas1r3*.

Sweet Taste Preferences and Alcohol Intake

Humans perceive certain concentrations of alcohol (ethanol) as sweet.[157] In rodents, perception of the sweet taste component of ethanol was shown in behavioural and neurophysiological experiments (reviewed by Bachmanov *et al.*[158]). In behavioural studies, conditioned taste aversion generalized between ethanol and sucrose.[159–162] Electrophysiological recordings indicate that lingual application of ethanol activates sweetener-responsive neural fibres in the gustatory nerves[163,164] and sweetener-responsive units in the nucleus of the tractus solitarius;[165,166] this activity is blocked by application of gurmarin, a peripheral antagonist of sweet taste.[166]

In addition to activation of peripheral mechanisms of sweet taste by ethanol, central mechanisms that determine hedonic responses to ethanol and sweeteners also overlap and involve opioidergic, serotonergic and dopaminergic brain neurotransmitter systems.[167–172] These neural pathways are also implicated in drug addiction, and there is evidence that in humans and rodents sweetener preference correlates with administration of drugs, such as cocaine and heroin.[173,174]

Several studies have shown that in humans sweet liking is associated with proclivity to drink more alcohol,[175–179] but genes responsible for this association are still unknown. Sweet taste phenotypes have a potential to be used as biological markers for diagnosing predisposition to alcoholism.[150,176,177,180]

Studies with rodents elucidated some genetic factors for the association between sweet taste and alcohol. In mice and rats, positive correlations between preferences for ethanol and sweeteners were found among various strains and in segregating crosses.[105,112,123,124,149,150,181–189] Genetic analysis of a cross between mice from a high ethanol- and sweetener-preferring C57BL/6ByJ strain and a low ethanol- and sweetener-preferring 129P3/J strain suggested that the strain differences in sweetener and ethanol consumption depend on relatively small and partially overlapping sets of genes.[124]

T1R-dependent Mechanisms

One of the genetic loci influencing alcohol preference in mice, *Ap3q* (alcohol preference 3 QTL), maps to a region of chromosome 4 overlapping with the *Tas1r3* gene.[190] This suggests that the *Tas1r3* gene is identical to the *Ap3q* locus. Consistent with this, allelic variation of the *Tas1r3* gene in congenic and knockout mice has pleiotropic effects on ingestive responses to sweeteners and ethanol in the long-term and brief-access tests, and influences taste quality perception of ethanol.[191–193] These data suggest that *Tas1r3* alleles influence perception of the sweet taste component of ethanol flavour. As a result, mice with a more sensitive variant of the sweet taste receptor perceive stronger sweetness from ethanol, which makes it more hedonically attractive and promotes ethanol intake.

T1R-independent Mechanisms

In addition to the *Tas1r3* gene, rodents have other genetic loci with pleiotropic effects on ethanol and sweetener intake.[194,195] To study T1R-independent mechanisms of association between ethanol and sweetener preferences, we used mice selectively bred for high and low saccharin intake, which have identical allele of the *Tas1r3* gene.[55,137] Mice selected for high saccharin intake had higher ethanol intakes and preferences than mice selected for low saccharin intake. Because these mice do not differ in peripheral taste input, we hypothesized that effects on sweetener and ethanol preference are mediated by the central mechanisms. Consistent with this, mice from the two strains differed in number of urocortin 1-containing cells in the brain Edinger–Westphal nucleus, which is involved in the regulation of ethanol consumption.[196] These differences are consistent with the involvement of central mechanisms in selection for sweetener intake and in correlated divergence in ethanol consumption. Therefore, this study has shown that genetic association between consumption of ethanol and sweeteners depends not only on the *Tas1r3* locus, but also on at least one other locus, which is involved in central mechanisms regulating ethanol and sweetener intake.

Concluding Remarks

The data presented in this review demonstrate that sweet taste has a complex genetic architecture. Variation of the sweet taste receptor genes contributes to differences in sweet taste perception within and between species. In addition to the sweet taste receptors, a number of other genes influence sweet taste responses. These genes are involved in different stages of sweet taste processing pathway, including peripheral and central mechanisms. There is evidence that responses to different sweeteners are affected by different sets of genes. Individual differences in sweet taste preferences are associated with predisposition to alcoholism.

In recent years, genetics has experienced dramatic progress, with genome sequencing completed for several species, including the mouse and the human. These advances in genomic resources tremendously facilitate genetic studies and make them an even more powerful approach for understanding mechanisms of sweet taste.

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