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# The sweet and the bitter of mammalian taste

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The discovery of two families of mammalian taste receptors has provided important insights into taste recognition and taste perception. Recent studies have examined the receptors and signaling pathways that mediate sweet, bitter, and amino acid taste detection in mammals. These studies demonstrate that taste cells are selectively tuned to different taste modalities and clarify the logic of taste coding in the periphery.

## Addresses

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## Abbreviations

<b>GPCR</b>	G protein-coupled receptor
<b>KO</b>	knockout
<b>mGluR</b>	metabotropic glutamate receptor
<b>MSG</b>	monosodium glutamate
<b>PLC</b>	phospholipase C
<b>PTC</b>	phenylthiocarbamide

## Introduction

Humans have a highly specialized gustatory system designed to detect submicromolar quantities of compounds that are noxious or toxic at one extreme and submolar concentrations of compounds that provide caloric energy at the other. Although the human tongue can recognize hundreds of different taste compounds, gustatory cues have classically been grouped into four or five categories: sweet, bitter, salty, sour, and glutamate (umami). How does the recognition of chemical cues result in the perception of a few different taste modalities?

Taste recognition in mammals is mediated by specialized epithelial cells that are arranged in taste buds on the tongue. Each taste bud contains approximately 50–100 taste cells and is innervated by multiple taste fibers that transmit taste cell activation in the periphery to changes in neural activity in the brain [1]. During the past 30 years, several studies on the properties of taste cells and their

connections have led to two opposing models for how taste information is encoded on the tongue [2–4]. In principle, individual taste cells could be tuned to one modality or multiple modalities. The ‘across-fiber patterning’ model of taste coding proposes that a single taste cell in the periphery recognizes a variety of different tastes and responds to multiple taste modalities. In this scenario, the broadly tuned responses of cells must be compared in the context of other cells firing in order for the brain to interpret what the tongue is tasting. An alternative model suggests that taste cells are selectively tuned to a specific taste modality; for example, some cells recognize sugars and others recognize bitter substances. In this ‘labeled line’ model of taste coding, different taste percepts would result from the activation of different cell types in the periphery.

The recent identification of mammalian taste receptor genes that recognize sugars, amino acids, and bitter compounds has provided the opportunity to critically evaluate these models. The aim of this review is to present a current perspective on taste coding, based on recent studies using receptors as molecular probes to examine the sense of taste.

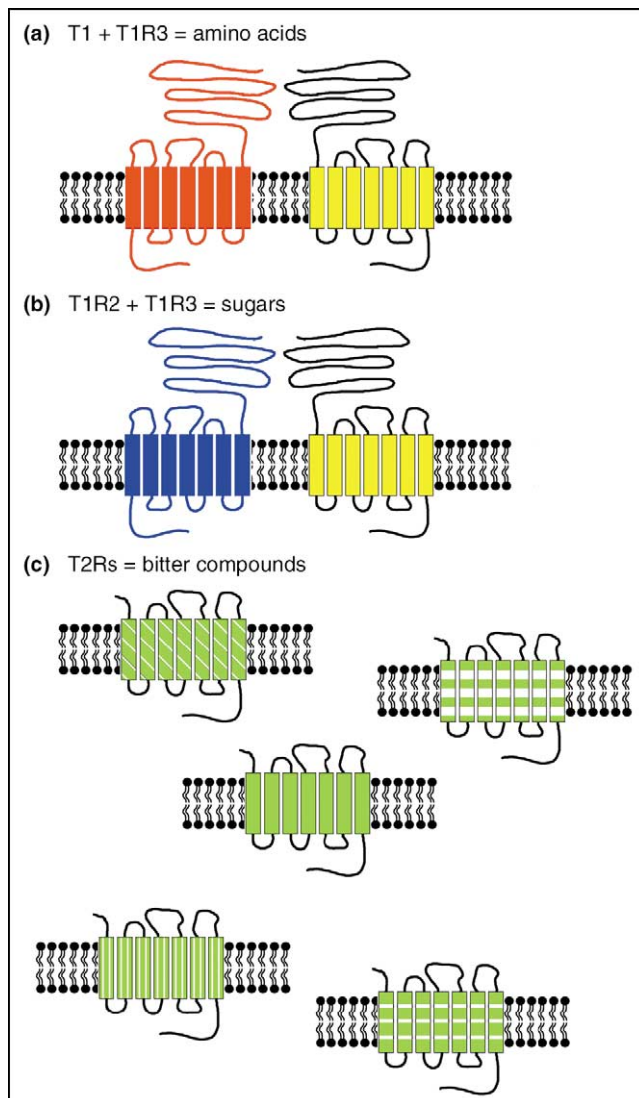
## Mammalian taste receptor families

Two families of mammalian taste receptor genes were recently identified using molecular and genomic approaches. These receptors are expressed in subsets of taste cells and participate in the recognition of sugars, amino acids, and bitter compounds (Figure 1).

The T1R family of taste receptors consists of three genes: T1R1, T1R2, and T1R3 [5–11]. These receptors belong to the type C family of G protein coupled receptors (GPCRs), along with metabotropic glutamate receptors (mGluRs) and  $\gamma$ -aminobutyric acid B (GABA $\beta$ ) receptors, and they are characterized by the presence of large extracellular amino-terminal domains that are proposed to be involved in ligand-binding. Interestingly, studies of receptor–ligand interactions in heterologous cells suggest that T1R receptors function as heteromers, with different T1R combinations recognizing different classes of tastes. The T1R1+3 subunits together function as a broadly tuned amino acid receptor [12<sup>\*\*</sup>,13<sup>\*\*</sup>], and the T1R2+3 subunits together function as a broadly tuned sweet receptor [10,13<sup>\*\*</sup>].

The second family of taste receptors is the T2R family of bitter receptors [14,15]. This family is distantly related to the opsin gene family, and contains approximately 30 genes. They are clustered at loci that had been previously

Figure 1



Two families of taste receptors recognize amino acids, sugars, and bitter compounds. (a) The T1R1 + T1R3 heteromer recognizes amino acids, (b) and the T1R2 + T1R3 heteromer detects sugars. (c) The 30 members of the T2R receptor family recognize bitter substances.

associated with bitter taste defects in humans and mice [16–19]. Studies of ligands that activate T2Rs in heterologous cells showed that T2Rs function as validated bitter taste receptors [20,21]. Surprisingly, the few T2Rs that have been studied recognize a small subset of bitter ligands. However, multiple T2Rs are co-expressed in the same cells [14], which suggests that a single cell recognizes a vast array of bitter cues.

### Sugar sensing by T1R2+3 cells

Are the T1Rs the only sweet receptors on the tongue? Several lines of evidence suggest that T1R2 and T1R3 together account for the recognition of all sugar substances. First, the combination of T1R2+3 recognizes

natural sugars, such as sucrose and glucose, and artificial sweeteners, such as saccharin and acesulfame-K, when expressed in heterologous cells [10,13<sup>\*\*</sup>]. Second, T1R2 and T1R3 knockout (KO) mice are defective in the ability to sense natural and artificial sugars during gustatory nerve recordings and behavioral taste preference assays [22<sup>\*</sup>,23<sup>\*\*</sup>]. Interestingly, the single KO animals show a residual response to high sugar concentrations that is eliminated in T1R2/T1R3 double KO animals [23<sup>\*\*</sup>]. This indicates that T1R2 and T1R3 homomeric receptors might act as low affinity sugar receptors, providing a greater range and complexity to sugar taste detection. Third, sequence variations in T1R genes from different species mechanistically explain species-specific sweet preferences. For example, although wild type mice do not recognize the artificial sweetener aspartame, mice that have been engineered to express the human T1R2 gene in place of the mouse T1R2 gene now detect aspartame as a sweet substance [23<sup>\*\*</sup>].

The finding that T1R2 and T1R3 recognize all sugar substances suggests that the perception of sweet is based on the activation of a single broadly tuned T1R2+3 receptor and perhaps T1R2 and T1R3 homomeric receptors. T1R2 is co-expressed with T1R3 in one cell population on the tongue, whereas other cells contain T1R3 alone [10], which suggests that these two cell populations are responsible for sugar detection.

### Amino acids sensing by T1R1+3

The taste of monosodium glutamate (MSG) is so revered among some as to warrant its own taste category, umami, and so feared among others that ‘No MSG’ signs are often used to advertise restaurants and dishes. Perhaps appropriately, the receptors that recognize this contentious taste have been the source of a controversy that finally finds resolution in several recent experiments on the role of T1R1+3 in umami taste.

For several years, a novel splice product of a metabotropic glutamate receptor (taste-mGluR4) has been proposed to be the umami receptor [24–26]. Taste-mGluR4 is detected in taste tissue by reverse transcriptase–polymerase chain reaction (RT–PCR) experiments and recognizes glutamate at millimolar concentrations when expressed in heterologous cells [24,25]. However, this receptor lacks the signal sequence required for proper membrane insertion as well as domains required for glutamate-binding in prototypical mGluRs [27]. Moreover, KO mice lacking mGluR4 still detect glutamate, in fact they are even super-tasters, showing enhanced glutamate detection [28].

The discovery that the T1R1+3 heteromeric receptor recognizes amino acids solves the conundrum of how umami is sensed *in vivo*. T1R1+3 is expressed in subsets of taste cells on the tongue and detects L-amino acids

(including glutamate) when expressed in heterologous cells [12<sup>••</sup>,13<sup>••</sup>]. Mice lacking T1R3 or T1R1 are severely defective in their ability to sense glutamate and other amino acids when tested using behavioral studies and gustatory nerve recordings [22<sup>•</sup>,23<sup>••</sup>]. A small response to MSG in these mice has led to the proposal that there are additional umami sensors [22<sup>•</sup>]. However, this response is eliminated upon inclusion of sodium blockers, which strongly suggests that the residual response is due to the sodium component of MSG rather than the glutamate component [23<sup>••</sup>]. These results establish T1R1+3 as the mammalian amino acid receptor and demonstrate its requirement for sensing umami taste. Interestingly, the human T1R1+3 preferentially recognizes glutamate at ten-fold lower concentrations than other amino acids, whereas the mouse T1R1+3 recognizes all amino acids with similar affinity [12<sup>••</sup>,13<sup>••</sup>], which suggests that the taste of umami is a human-specific taste preference.

The expression patterns of T1R genes reveal that T1R1 is co-expressed with T1R3 in cells that do not contain T1R2 [10]. This demonstrates that amino acid receptors and sugar receptors are found in different cell types on the tongue, consistent with the labeled line model of taste coding.

### Bitter taste mediation by T2Rs

On the basis of functional studies of individual T2Rs expressed in heterologous cells, it is proposed that the 30 members of the T2R receptor family encode bitter receptors [20]. Knockout mice lacking specific T2Rs have not yet been reported to define the function of these genes *in vivo*. However, naturally occurring polymorphisms in T2Rs are associated with bitter taste defects. For example, mice that cannot detect cycloheximide have polymorphisms in T2R5 [20]. In addition, humans vary in their ability to detect the bitter substance phenylthiocarbamide (PTC) and individual PTC taste variation can be accounted for by polymorphisms in a T2R gene [29<sup>••</sup>,30]. Other T2Rs show polymorphisms that might account for individual differences in bitter detection [31].

Most or all T2Rs are co-expressed in one cell population on the tongue that does not contain T1Rs [10,14]. This indicates that cells with T2Rs recognize a wide range of structurally diverse bitter compounds by virtue of having a large number of receptors. By contrast, cells with T1Rs detect a large number of sugars because a single T1R heteromeric receptor is broadly tuned. In each case, broadly tuned cells might limit taste discrimination, which suggests that mammals can distinguish sweet from bitter, but cannot finely distinguish different bitter compounds.

### Taste quality encoding by modality-specific taste cells

The picture that is emerging from studies of the T1R and T2R receptor families is that taste information in the

periphery is parceled into a small number of categories. The T2R bitter receptors, the T1R1+3 amino acid receptor, and the T1R2+3 sugar receptor are segregated into different cells on the tongue [10,14], which suggests that there are sweet cells, amino acid cells, and bitter cells. Moreover, the loss of the T1R2 sugar receptor does not affect amino acid, bitter, or salt detection and the loss of the T1R1 amino acid receptor does not affect sugar, salt, or bitter detection [23<sup>••</sup>], which is consistent with the notion that taste is carried along labeled lines.

Two other recent experiments with KO mice provide strong support for the labeled line model of taste coding. Recently, the signal transduction components phospholipaseC $\beta$ 2 (PLC $\beta$ 2) and the TRPM5 ion channel have been shown to be expressed in taste cells [32–34,35<sup>•</sup>]. They are essential for all bitter and sweet taste detection, with no other signaling cascade acting independently [36<sup>••</sup>]. This is in sharp contrast with former models of taste transduction that involved almost all of the known second messenger systems (PLC-mediated, phosphodiesterase-mediated, and adenylate cyclase-mediated) as well as several classes of ion channels for bitter and sweet taste detection [1,37–40].

Mice lacking PLC $\beta$ 2 do not detect bitter or sweet substances [36<sup>••</sup>]. If these two modalities are housed in different cells and operate independently, then the rescue of one modality should not affect the other. A transgene containing PLC expressed under the control of a T2R bitter promoter was introduced into PLC KO mice [36<sup>••</sup>]. Interestingly, it rescued the response to bitter but not to sweet, providing direct support that bitter and sweet receptors are not co-expressed in the same cells and that the two modalities are recognized independently.

In a second beautifully done experiment to test the function of different taste cells, a synthetic GPCR that is activated by a non-natural ligand but that couples to endogenous taste pathways was introduced into T1R2 taste cells [23<sup>••</sup>]. To test if activation of T1R2 cells is sufficient to generate a sweet taste response, mice were given the choice between water and water with the non-natural ligand. When the synthetic GPCR is expressed in T1R2 cells, mice show a strong taste preference for the non-natural, formerly innocuous ligand.

This is an important result because it shows that activation of a single cell-type is sufficient to generate a behavior, which suggests that cells are hardwired to stereotyped behaviors. It also strongly argues against the notion that cells respond to multiple taste modalities, as in that case artificial activation would be unlikely to produce a specific response. Temporal coding models, in which the timing and patterns of action potentials are the distinguishing features of different tastes, are also unlikely, again because artificial stimulation would not

mimic endogenous activation. The most parsimonious model is that taste information is carried along labeled lines, with different pathways for attractant and avoidance responses.

## Conclusions

The identification of taste receptors and the signaling pathway that they use has provided insight into taste recognition and taste perception. T1Rs recognize sugars and amino acids, T2Rs recognize bitter substances, and both receptor families converge on a common signaling pathway that utilizes PLC $\beta$ 2 and TRPM5. Receptors are selectively expressed in subsets of cells such that different taste cells respond to different categories of tastes. Thus, our perception of four or five taste modalities might result from the activation of four or five different cell types on the tongue that transmit this activation along labeled lines to the brain. The past five years have brought the powerful combination of molecular biology, electrophysiology, genetics, and behavior to bear on the problem of peripheral taste and revolutionized the taste field. Future studies will undoubtedly apply these approaches to examine how taste information is processed in the central nervous system.

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