

## Molecular Mechanisms of Bitter and Sweet Taste Transduction\*

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The sense of taste plays a critical role in the life and nutritional status of humans and other organisms. Human taste perception may be categorized according to four well known and widely accepted descriptors, sweet, bitter, salty, and sour (corresponding to particular taste qualities or modalities), and two more controversial qualities: fat and amino acid taste. The ability to identify sweet-tasting foodstuffs is particularly important as it provides us and other vertebrates with a means to seek out needed carbohydrates with high nutritive value. The perception of bitter, on the other hand, is essential for its protective value, enabling humans to avoid potentially deadly plant alkaloids and other environmental toxins. The focus of this review is on recent advances in our understanding of the transduction elements and signaling mechanisms underlying bitter and sweet taste transduction (see Fig. 1).

The sensations of bitter and sweet tastes are initiated by the interaction of sapid molecules (“tastants”) with G protein-coupled receptors (GPCRs)<sup>1</sup> in the apical membranes of taste receptor cells (TRCs). TRCs are specialized epithelial cells with many neuronal properties including the ability to depolarize and form synapses. TRCs are typically clustered in groups of ~100 within taste buds. The apical surface of TRCs, which makes contact with the oral cavity, is rich in convoluted microvilli containing GPCRs, ion channels, and other transduction elements. The basolateral aspect of TRCs contains ion channels and synapses with afferent taste nerves.

### Bitter Transduction

*Receptors*—“Data mining” of the National Center for Biotechnology Information DNA sequence data bases was used to identify an ~25-member multigene family of TRC-expressed GPCRs, named T2Rs or TRBs (so-called as the second family of taste receptors identified) (1, 2). The T2R/TRB GPCRs map to regions of human and mouse chromosomes implicated genetically in sensitivity to various bitter compounds (3–5). T2R/TRB receptors are only distantly related to other GPCRs such as the V1R vomeronasal receptors and display 30–70% identity

within the gene family. These receptors have the greatest conservation in their cytoplasmic loops and their adjacent transmembrane segments (predicted sites of G protein interaction) and the greatest divergence in their extracellular regions (potential regions of ligand binding).

In rat and mouse T2R/TRB receptors are expressed in ~15–20% of TRCs in taste buds of the circumvallate and foliate papillae and the palate but in very few TRCs in fungiform papillae (1). Based on *in situ* hybridization with mixed *versus* individual T2R/TRB probes it was concluded that most T2R/TRB receptors are expressed in the same TRCs (1, 2). T2R/TRB receptors are only found in TRCs positive for expression of gustducin (a G protein implicated in bitter taste) (see Fig. 2) (1).

One murine T2R/TRB receptor (mT2R5), when expressed in heterologous cells, responded to bitter cycloheximide at a concentration comparable with the murine threshold for aversion (6). mT2R5 was found to couple selectively to  $\alpha$ -gustducin *versus* other G protein  $\alpha$ -subunits. Taste responses were obtained from only one other T2R/TRB-transfected cell; a human/mouse orthologous pair, hT2R4/mT2R8, apparently encodes a receptor responsive to denatonium and 6-*n*-propyl-2-thiouracil. However, the concentration of denatonium required to stimulate this receptor was more than 3 orders of magnitude higher than the human threshold for detection, suggesting that another GPCR is likely to be the “denatonium” receptor.

*G Proteins and Effector Enzymes*— $\alpha$ -Gustducin is an  $\alpha$ -transducin-like G protein  $\alpha$ -subunit selectively expressed in ~25–30% of TRCs (7, 8). *In vitro* biochemical assays and *in vivo* analysis of  $\alpha$ -gustducin knockout mice have shown that  $\alpha$ -gustducin is involved in bitter taste transduction (9, 10).  $\alpha$ -Gustducin knockout mice show markedly reduced behavioral and/or nerve responses to the bitter compounds denatonium benzoate, quinine sulfate, cycloheximide, and tetraethylammonium (10).<sup>2</sup> Effector-interacting peptides derived from  $\alpha$ -transducin that mimic the action of activated transducin/gustducin activate a taste phosphodiesterase (PDE) (11), recently identified as PDE1A.<sup>3</sup> Rapid quench flow studies plus or minus antibodies directed against  $\alpha$ -gustducin have shown that many bitter compounds lead to a gustducin-mediated decrease in taste tissue cyclic nucleotide (cNMP) levels (12).

In response to bitter compounds, the  $\beta\gamma$ -subunits of gustducin (identified as  $G\beta_3$  and  $G\gamma_{13}$ ) mediate an increase in taste tissue levels of inositol trisphosphate ( $IP_3$ ) and diacylglycerol (DAG) (13, 14). This response is blocked by antibodies directed against  $G\beta_3$ ,  $G\gamma_{13}$ , or  $PLC\beta_2$  (13–15), implicating all three of these proteins in this taste response; control antibodies or antibodies directed against  $\alpha$ -gustducin had no effect on  $IP_3$  or DAG generation. Consistent with their role in an  $IP_3$ /DAG taste signaling pathway  $\alpha$ -gustducin,  $G\beta_3$ ,  $G\gamma_{13}$ , and  $PLC\beta_2$  are co-expressed in large part in TRCs (16, 17).

In addition to  $\alpha$ -gustducin several G protein  $\alpha$ -subunits have been identified in TRCs (e.g.  $G\alpha_{i-2}$ ,  $G\alpha_{i-3}$ ,  $G\alpha_{14}$ ,  $G\alpha_{15}$ ,  $G\alpha_q$ ,  $G\alpha_s$ , and  $\alpha$ -transducin (7, 11, 18)). One or more of these G protein  $\alpha$ -subunits may play a role in bitter taste transduction because  $\alpha$ -gustducin knockout mice retain residual responsiveness to

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<sup>1</sup> The abbreviations used are: GPCR, G protein-coupled receptor; *dpa*, D-phenylalanine taste sensitivity locus;  $IP_3$ , inositol trisphosphate; PDE, phosphodiesterase; cNMP, cyclic nucleotide monophosphate; PLC, phospholipase C; *sac*, saccharin taste sensitivity locus; TRC, taste receptor cell; DAG, diacylglycerol; RT, reverse transcription.

<sup>2</sup> V. Danilova, Y. Danilov, S. Damak, R. F. Margolskee, and G. Hellekant, unpublished results.

<sup>3</sup> M. M. Bakre, J. L. Glick, S. D. Rybalkin, M. Max, J. A. Beavo, and R. F. Margolskee, unpublished results.

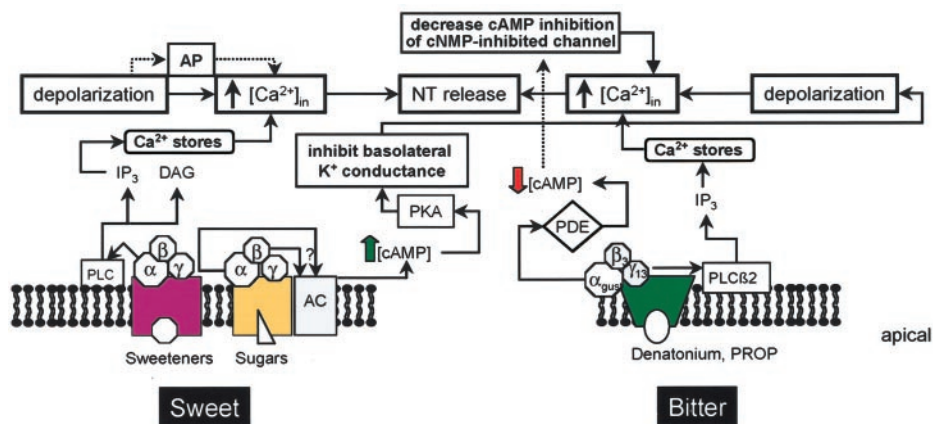


FIG. 1. **Proposed transduction mechanisms in vertebrate taste receptor cells underlying bitter and sweet taste qualities.** All transduction pathways are proposed to converge on common elements that mediate a rise in intracellular  $\text{Ca}^{2+}$  followed by neurotransmitter (NT) release. Artificial sweeteners activate GPCRs (T1R heterodimers) apparently linked via PLC to  $\text{IP}_3$  production and release of  $\text{Ca}^{2+}$  from intracellular stores. Sugars activate GPCRs (T1R heterodimers) apparently linked via adenylyl cyclase (AC) to cAMP production, which in turn may inhibit basolateral  $\text{K}^+$  channels through phosphorylation by cAMP-activated protein kinase A (PKA). Bitter compounds, such as denatonium and 6-*n*-propyl-2-thiouracil (PROP), activate particular T2R/TRB isoforms, which activate gustducin heterotrimer. Activated  $\alpha$ -gustducin stimulates PDE to hydrolyze cAMP; the decreased cAMP may disinhibit cyclic nucleotide-inhibited channels to elevate intracellular  $\text{Ca}^{2+}$ .  $\text{G}\beta\gamma$  subunits (e.g.  $\beta_3\gamma_{13}$ ) released from activated  $\alpha$ -gustducin activate  $\text{PLC}\beta_2$  to generate  $\text{IP}_3$ , which leads to release of  $\text{Ca}^{2+}$  from internal stores. AP, action potentials. See text for additional details. Modified from Gilbertson *et al.* (48).

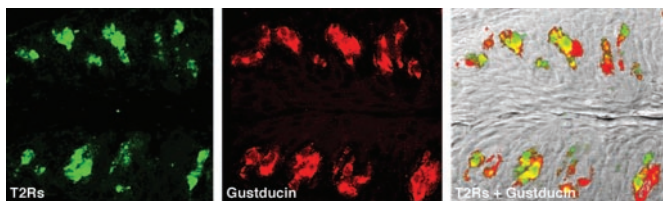


FIG. 2. **Double-label fluorescent *in situ* hybridization demonstrates that T2R/TRB receptors (T2Rs) are expressed in the same cells with  $\alpha$ -gustducin (Gustducin).** Modified from Adler *et al.* (1).

bitter compounds (10). Furthermore, transgenic expression of a dominant-negative form of  $\alpha$ -gustducin from the gustducin promoter further decreased the residual responses of  $\alpha$ -gustducin knockout mice, apparently by inhibiting T2R/TRB interactions with other TRC-expressed G protein  $\alpha$ -subunits.

**Transduction Pathways**—Gustducin heterotrimers that have been activated by bitter-stimulated T2R/TRB receptors mediate two responses in TRCs: a decrease in cNMPs via  $\alpha$ -gustducin and a rise in  $\text{IP}_3$ /DAG via  $\beta\gamma$ -gustducin. The subsequent steps in the  $\alpha$ -gustducin-PDE-cNMP pathway are presently uncertain (reviewed in Ref. 19); decreased cNMPs may act on protein kinases, which in turn may regulate TRC ion channel activity, or cNMP levels may regulate directly the activity of cNMP-gated (20) and cNMP-inhibited (21) ion channels expressed in TRCs. The subsequent steps in the  $\beta\gamma$ -gustducin-PLC- $\text{IP}_3$ /DAG pathway are apparently activation of  $\text{IP}_3$  receptors (type 3  $\text{IP}_3$  receptors have recently been shown to be co-expressed in TRCs with  $\text{G}\gamma_{13}$  and  $\text{PLC}\beta_2$  (16, 17)) and release of  $\text{Ca}^{2+}$  from internal stores followed by neurotransmitter release (22). These pathways are diagrammed in Fig. 1.

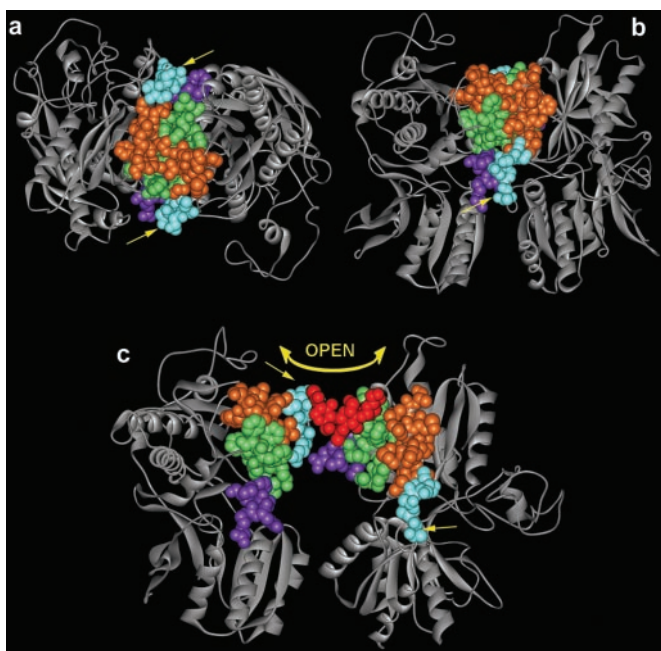
### Sweet Transduction

**Receptors**—The receptors underlying sweet taste have only just now been identified based on earlier genetic mapping of sweet taste response loci (23–26) and recent data mining of human and mouse DNA sequence data bases (27–30). It has been known for some three decades that inbred strains of mice such as C57BL/6 and DBA/2 differ markedly in their ingestive responses to solutions containing the artificial sweetener saccharin (31, 32). The murine loci for *sac* (determines preference and electrophysiological responsiveness to saccharin, sucrose,

and other sweeteners) and *dpa* (determines preference and responsiveness to D-phenylalanine) were known to be the major genetic factors that determine differences between sweet-preferring and sweet-indifferent strains of mice (5, 33–35). Fuller (33) first proposed the existence of a single saccharin preference gene, *sac*, to explain the differences exhibited by C57BL/6 and DBA/2 to ingestion of solutions of saccharin covering a wide concentration range. Both *dpa* and *sac* were shown to affect peripheral nerve responses to sucrose (24), suggesting that either or both genes might encode a taste receptor or some other taste transduction element. *sac* has been mapped to the distal end of mouse chromosome 4, and *dpa* has been mapped to proximal 4 (23–26).

In one approach to identify candidates for *sac*, all genes present within a region of  $\sim 1$  million base pairs of the sequenced human genome syntenous to the *sac* region of mouse were identified and ordered into a contiguous stretch of DNA (a “contig”) (27). From this search T1R3 (human taste receptor family 1, member 3), a previously unknown GPCR and the only GPCR in this region of the genome, was identified as the most likely candidate for *sac*. T1R3 is  $\sim 30\%$  related to T1R1 and T1R2, two “orphan” GPCRs selectively expressed in TRCs (36). T1R3 was also identified independently in searches for novel TRC-expressed GPCRs that mapped to the region of the human genome syntenous to the murine *sac* region (28, 30), as well as by an RT-PCR search for novel taste receptors (29). As befits a taste receptor, T1R3 and/or the murine ortholog (T1r3) were shown to be expressed selectively in TRCs within fungiform, foliate, and circumvallate papillae (27–30). Double *in situ* hybridization showed that T1r3 was co-expressed with T1r1 in anterior TRCs and with T1r2 in posterior TRCs (28, 37).

By comparing the sequence of T1r3 from several independently derived strains of mice, eight amino acid polymorphisms were identified; however, only two of these polymorphisms differentiated all taster strains of mice from all non-taster strains (27–30, 37). These two polymorphisms occur within a specific portion of the N-terminal extracellular region of T1r3 that (based on homology with mGluR1 (metabotropic glutamate receptor 1) and the known structure of the N-terminal domain of mGluR1 (38)) is predicted to be involved in GPCR dimerization. T1r3 from non-tasters is predicted to contain an extra N-terminal glycosylation site that according to models of the structure of T1r3 would preclude its hetero- or homodimer-



**FIG. 3. The three-dimensional structure of the N-terminal domain of murine T1r3 was modeled based on the solved structure of the N-terminal domain of mGluR1 (38).** The model shows a T1r3 homodimer. Based on recent results (37) it is likely that T1r3 also heterodimerizes with T1r2 and T1r1. *a*, the view from the “top” of the dimer looking down from the extracellular space toward the membrane. *b*, the T1r3 dimer viewed from the side. In this view the transmembrane region (not displayed) would attach to the bottom of the dimer. *c*, the T1r3 dimer is viewed from the side as in *b*, except the two dimers have been spread apart (indicated by the *double-headed arrow*) to reveal the contact surface. A space-filling representation (colored *red*) of three glycosyl moieties (*N*-acetylgalactose-*N*-acetylgalactose-mannose) has been added at the novel predicted site of glycosylation of non-taster mT1R3. Note that the addition of even three sugar moieties at this site is sterically incompatible with dimerization. Regions of mT1R3 corresponding to those of mGluR1 involved in dimerization are shown by space-filling amino acids. The four different segments that form the predicted dimerization surface are *color-coded*. The portions of the two molecules outside of the dimerization region are represented by a *backbone tracing*. The two polymorphic amino acid residues of T1r3 that differ in taster *versus* non-taster strains of mice are within the predicted dimerization interface nearest the N terminus (colored *light blue*). The additional *N*-glycosylation site at amino acid 58 unique to the non-taster form of T1r3 is indicated in each *panel* by the *straight arrows*. Modified from Max *et al.* (27).

ization (see Fig. 3) (27). The conclusion from the earlier studies (27–30) was that T1r3 is a strong candidate for *sac*, and based on the molecular models it was predicted to be a sweet-responsive (*i.e.* sweet-liganded) taste receptor (27). Furthermore, it was predicted that the related T1r1 and T1r2 receptors would also be involved in sweet or amino acid taste (27). Confirmation that T1R3 is *sac* has come recently from the conversion of non-taster mice into tasters by the transgenic expression of T1R3 from a taster strain (37).<sup>4</sup> Heterologous expression of T1r3 in combination with T1r2 demonstrated that this heterodimer comprises a functional taste receptor responsive to several natural and artificial sweeteners (37). Heterologous expression of T1r3 or T1r2 alone did not yield sweet-responsive cells, suggesting that a T1r3/T1r2 heterodimeric form is required to manifest a functional sweet receptor. Presumably, T1r3/T1r1 heterodimers form to generate functional taste receptors; however, heterologous expression of T1r1 alone or T1r1-containing heterodimers has failed to date (37).

*G Proteins and Effector Enzymes*—Several biochemical and

electrophysiological studies have implicated  $G_s$ , adenylyl cyclase, and cAMP in TRC responses to sweet tastants (39–46); one study has implicated  $PLC\beta_2$  and  $IP_3/DAG$  in sweet taste (22) (for further details see Fig. 1 and “Transduction Pathways” below). Gustducin may be involved in sweet as well as in bitter responses;  $\alpha$ -gustducin knockout mice show diminished behavioral and/or electrophysiological responses to many sweet compounds including sucrose, proline, tryptophan, and the artificial sweeteners saccharin, acesulfame K, and SC45647 (10).<sup>2</sup> Although gustducin could be activated by taste receptor-containing membranes plus bitters, neither sucrose nor artificial sweeteners activated gustducin in the presence of these membranes (9, 11). Interestingly, several artificial sweeteners competitively inhibited bitter receptor activation of gustducin suggesting potential cross-talk between bitter and sweet receptors (47). It has not yet been determined which G protein  $\alpha$ - and  $\beta\gamma$ -subunits couple with the T1r receptors; any G protein subunits that are selectively co-expressed with T1r receptors would be candidates for coupling T1r receptors to downstream transduction pathways. Double *in situ* hybridization indicates that only 10–20% of T1r3-positive TRCs are also positive for  $\alpha$ -gustducin (28); however, single-cell RT-PCR with T1r3 probes and immunohistochemistry with an anti-T1R3 antibody indicated that about two-thirds of T1r3/T1R3-positive TRCs are  $\alpha$ -gustducin-positive (27). The discrepant results obtained by these different techniques may be because of differences in sensitivity. The effector enzymes and second messengers in T1r-mediated sweet pathways are not known at present.

*Transduction Pathways*—Based on biochemical and electrophysiological studies of taste cells (22, 39–46) two models for sweet transduction have been proposed. The first is a GPCR- $G_s$ -cAMP pathway; sucrose and other sugars lead to activation of  $G_s$  via one or more coupled GPCRs (presumably T1r heterodimers); receptor-activated  $G\alpha_s$  activates adenylyl cyclase to generate cAMP; cAMP may act directly to cause cation influx through cNMP-gated channels or act indirectly to activate protein kinase A, which phosphorylates a basolateral  $K^+$  channel, leading to closure of the channel, depolarization of the taste cell, voltage-dependent  $Ca^{2+}$  influx, and neurotransmitter release. The second is a GPCR- $G_q/G\beta\gamma$ - $IP_3$  pathway; artificial sweeteners presumably bind to and activate one or more GPCRs (T1r heterodimers?) coupled to  $PLC\beta_2$  by either the  $\alpha$  subunit of  $G_q$  or by  $G\beta\gamma$  subunits; activated  $G\alpha_q$  or released  $G\beta\gamma$  activates  $PLC\beta_2$  to generate  $IP_3$  and DAG;  $IP_3$  and DAG elicit  $Ca^{2+}$  release from internal stores, leading to depolarization of the TRC and neurotransmitter release. These two pathways (diagrammed in Fig. 1) coexist in the same TRCs; sweet-responsive TRCs from rat circumvallate papillae had an influx of  $Ca^{2+}$  in response to sucrose, whereas the artificial sweeteners saccharin and SC45647 elevated  $Ca^{2+}$  via release from internal stores (22). These sweet-responsive TRCs did *not* respond to any bitter stimuli (22). Now that the sweet-responsive T1r receptors have been cloned and expressed it should be possible to definitively test these various models of sweet transduction. It is presently unclear how these receptors could selectively mediate cAMP responses to sugars and  $IP_3$  responses to artificial sweeteners.

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