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# Sweetness chemoreception theory and sweetness transduction

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**Abstract**

This review summarizes the outcome of sweet taste chemoreception research over the last 30 years. Since the sweet taste receptor has yet to be isolated and identified, several models have been developed to account for sweetness and to explain how molecules are structured to elicit sweet taste chemoreception. The models proposed are classified as follows: category I: the receptor binding theories AH-B, AH-B-X; AH-B-$\gamma$; the multi-attachment theory; the $\alpha$-helix protein theory; category II: the direct G-protein binding theory. All currently established hypotheses are discussed and their ability to account for the sweetness of a variety of structurally dissimilar compounds critically evaluated. After 30 years, the AH-B theory still appears to be the best explanation for the ligand binding chemistry that induces sweet taste response, and it is also consistent with prevailing sweet taste transduction hypotheses.


## 1. Introduction

A prevailing hypothesis for decades has been that the perception of sweetness is initiated by a chemical reaction between a ligand and a receptor on the surface of a taste cell. In 1967 two of us proposed that the ligands involved in this reaction must have a bipolar functional group capable of forming a cyclic hydrogen bonded transition state (Shallenberger & Acree, 1967).

The rationale was that hydrogen bonds in the receptor protein were disrupted in the transition state and that this was the mechanism for an allosteric change in the receptor protein inside the cell (Shallenberger & Acree, 1971). Presumably, because there is no objective measure of sweetness for making correlations with intracellular events, the resulting transduction process amplified the effect of the reaction by releasing multiple ions that depolarized the cell initiating a neural signal. Thirty years ago there was little evidence to support the details of this hypothesis other than structure–activity relationships (SAR) observed for sweet tasting compounds. However, recent studies of non-human chemosensory systems have yielded some very detailed information that may apply to humans (Bernhardt, Naim, Zehavi & Lindemann, 1996; Kinnamon & Margolskee, 1996; Naim & Striem, 1998), although it can never be known for certain that the events that occur are related to the fact that, to the human, the compounds taste sweet.

## 2. Sweet taste physiology

The chemosensory transduction system, found in most organisms, is associated with heterotrimeric nucleotide-binding G-proteins that produce a second messenger cascade of cyclic adenosine monophosphate (cAMP), inositol 1,4,5-triphosphate ($IP_3$) or diacylglycerol (DAG). These second messengers induce depolarization by modulating the ionic composition of the cell, usually through an increase in $Ca^{2+}$ concentration. The similarity in the amino acid composition of the G-proteins with similar function (olfactory, hormonal, etc.) but from different organisms (human, rat, mouse, chick, etc.) is common among those that have been successfully cloned and sequenced. No sweet taste-associated G-proteins have yet been cloned so it is not known how they are or may be related to each other.

However, if both human and rodent taste-associated G proteins show similar homology, then some of the properties of the human system may be predictable from the behavior of rodent models.

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In order to explain the initial chemistry of the transduction mechanism in rodents, three proposals have been made based on results from electrophysiological imaging, cytoplasmic imaging and behavioral studies. These proposals are summarized below:

1. The sugar receptor (SR) mechanism: a cellular response is brought about by a specific 7-transmembrane receptor protein, coupled to a G-protein and a second messenger cascade. Certain polyol structures (sweet ligands) interact with the protein receptors causing a G protein to release the intracellular second messenger cAMP (Hepler & Gilman, 1992).
2. The glycine receptor (GR) mechanism: amino acid-like ligands bind to a second 7-transmembrane receptor protein interacting with another G-protein to release the intracellular second messenger $IP_3$ or DAG (Naim, Bernhardt, Zehavi & Levinson, 1996).
3. The direct G-protein interaction (DGI) mechanism: certain "amphiphilic" compounds (having both polar and non-polar functions) penetrate the cell and interact with the G proteins causing second messenger release, usually $IP_3$, in much the same way that some drugs behave pharmacologically (Naim et al., 1996).

### 2.1. Structure–activity relationships

The first two of these mechanisms, SR and GR, require that the specificity of the ligand binding be different so that different ligands bind to different receptor proteins, despite evidence that both receptors are active on the same cell (Naim et al., 1996). What is the survival advantage of detecting both amino acids and sugars with the same sensory cells? Obviously both are valuable nutrients and being attracted to them is advantageous. Furthermore, the receptor protein need only differ in some chiral or topological feature while at the same time causing similar allosteric changes inside the cell. Relating the structure of sweet tasting molecules to their sensory properties, a process often called structure–activity relationship (SAR) modeling, is the most commonly used tool to generate hypotheses about ligand binding in human systems, primarily because it is non-invasive. The four most frequently mentioned SAR models, consistent with both SR and GR receptor mechanisms, are listed below.

#### 2.1.1. The bipolar hydrogen bonding or AH-B theory (Shallenberger & Acree, 1967)

This suggests that all sweet-tasting compounds contain a hydrogen bond donor (AH) and a hydrogen bond acceptor (B), separated by a distance of 2.5 to 4.0 Å that reacts with a complimentary AH-B pair on the receptor, forming two hydrogen bonds and/or interrupting an intramolecular hydrogen bond on the receptor protein. To adapt the AH-B tenet to the varying sweetness of amino acid enantiomers, Shallenberger, Acree, and Lee (1969) proposed that a spatial barrier, erected 3 Å removed, but perpendicular to receptor AH-B, can account for the D, L-amino acid tastes (Fig. 1). This distance was chosen so that tasteless L-amino acids with side chains longer than the ethyl group (L-alanine) would not fit on the site. The steric barrier was the simplest way to account for the sweetness of glycine. The presence of three or more points of attachment by the ligand could not be ruled out as an explanation of the chirality of the sweet response. However, the sweetness of glycine indicated that such additional attachment points are not necessary for the taste of amino acids.

The observations (Birch, 1976; Birch & Shamil, 1988) that sugars possess a primary AH, B unit, and that the bitterness of mannose lies at one end of the molecule while the sweetness resides at the other end, strongly support such an initial sweet-taste interaction chemistry. These observations were applied in developing the role of symmetry attributes in governing both the sweetness and bitterness of substances (Shallenberger, 1993, 1998). Because solubility in water is prerequisite for any taste, the role of water in the initiation of taste is also obviously of great importance (Birch, Karim, Lopez, Chavez & Morini, 1993), and one promising area of study is directed toward the probable taste role of the molar volume of a substance. The fact that the sugars, for example, have the same apparent specific volumes seems consistent with their general pure taste quality (Birch, Parke, Siertsema & Westwell, 1996), and therefore seems to be related to taste quality.

#### 2.1.2. The three-point attachment theory AH-B-γ

To account for the stereochemical specificity shown towards the enantiomeric amino acids Kier (1972) proposed that there is a third component in the sweetness

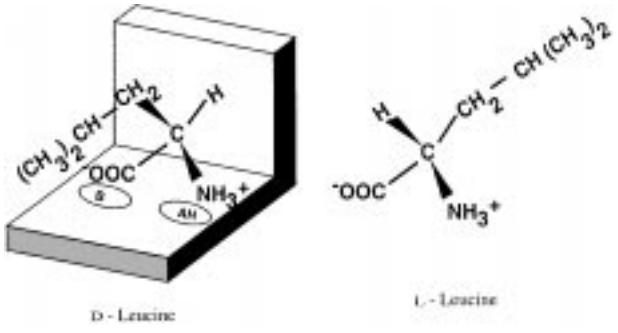


Fig. 1. A receptor spacial barrier to prevent L-leucine from interacting with the receptor AH,B unit. (after Shallenberger, 1996).

glycophore, designated X. Kier noted that a group high in electron density occurred in the same position with respect to the zwitterionic functions (AH-B). Kier assumes that a potent sweetener must interact with the sweetness receptor through three interactions, two by the means of hydrogen bonding according to Shallenberger and Acree (1967) and the third by means of dispersion (van der Waals) or hydrophobic interaction. Because X can also function as a lipophilic site, it is hereafter designated as γ. As applied to the difference in sweetness of D- and L-leucine, all three glycophore components AH-B,γ are hypothesized to bind to the receptor site as shown for D-leucine in Fig. 2. L-leucine would not fit on this site. However, glycine does taste sweet, presumably by binding to the AH,B portion, indicating that binding at γ is not required for transduction to be triggered.

The proposed role of the γ, γ interactions is to increase the affinity of an amino acid with an AH-B glycophore at the receptor site, thus increasing the sweet taste potency. Alternatively, Mathlouthi, Bressan, Portmann and Serghat, (1993) proposed that the more intense the glycophore hydrophobic/hydrophilic interaction is, the more mobile the molecules of water around it are, and this leads, in turn, to more intense sweetness. One final innate feature that γ may possess is that it has potential for an inductive effect on the electronic character of AH-B. Therefore, if γ is not required for binding it may function to modulate the potency of the ligand. It would seem that it is also in this sense that γ serves to enhance the sweetness potency of substances. That the degree of enhancement is governed by the distance and position of γ from AH-B is evident from observations on the taste of aspartame analogues (Ebeling, 1998). Goodman, Coddington and Mierke (1987) sought to deduce basic principles of taste perception from consideration of the energy-minimized structures and the tastes of a series of dipeptide isomers and derivatives. It was found that the structures of sweet-tasting dipeptides adopt the L-shape shown in Fig. 3 while their retro-inverso analogues do not. Only the L,L-isomer of aspartame tastes sweet, since only this isomer can adopt the L-shape prerequisite for sweet taste while the other three isomers are bitter.

A school of study (Mathlouthi et al., 1993) that is directed toward the role of water structure in taste, has proposed a three-step mechanism for the initiation of taste. The hydrophobic component of the tripartite glycophore is believed to impart a final hydrophobic/hydrophilic interaction wherein, the more strongly opposed the interaction is, the more mobile the water molecules around it are. Hence, the sweet taste intensity is enhanced.

### 2.1.3. The multi-point attachment theory

The most detailed and complex model of the sweet receptor was postulated by Tinti and Nofre (1991) from the SAR of the taste of all sweet substances, while Belitz used molecular modeling to generate a similar model. Tinti and Nofre (1991) suggested that there are at least eight functional categories that contribute to sweetness and that these are grouped into high affinity (activity) and secondary sites. They assumed that the sweetness receptor, in its resting state (R state), must be in a contracted conformation (C conformation) as the result of ionic and H-bonding interactions occurring between several recognition sites (Fig. 4).

When a sweetener interacts with the receptor it splits the ionic and H-bonding interactions in the sites, triggering profound conformational changes in the receptor and allowing it to expand. Presumably, it is this allosteric effect that initiates transduction. Sweetness potency can then be correlated with the number of additional sites involved at the receptor during interaction. This is consistent with the role of γ as an amplifier of potency but unnecessary for sweetness. It explains how glycine can bind to a chirally discriminatory receptor if the multiattachment models are chiral.

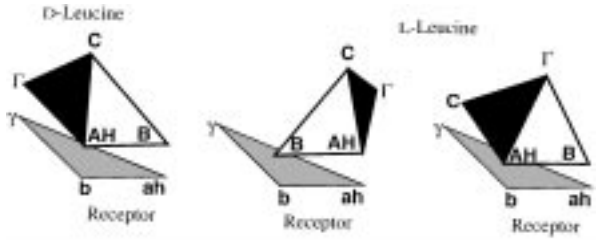


Fig. 2. Interaction of D-leucine with a sweetness receptor and the inability of the enantiomer to interact with the receptor due to steric hindrance by the L-amino acid's side chain (C) (after Shallenberger, 1996).

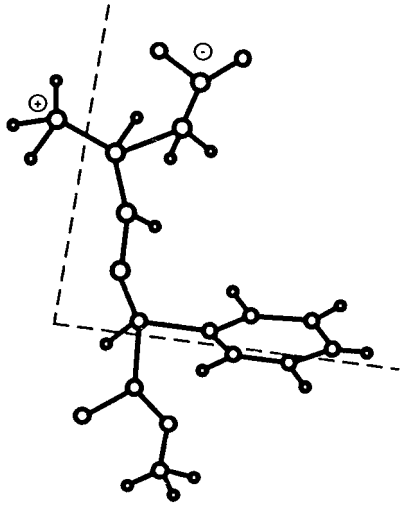

Fig. 3. Required L-shaped molecule for sweet aspartyl compounds (after Goodman et al., 1987).

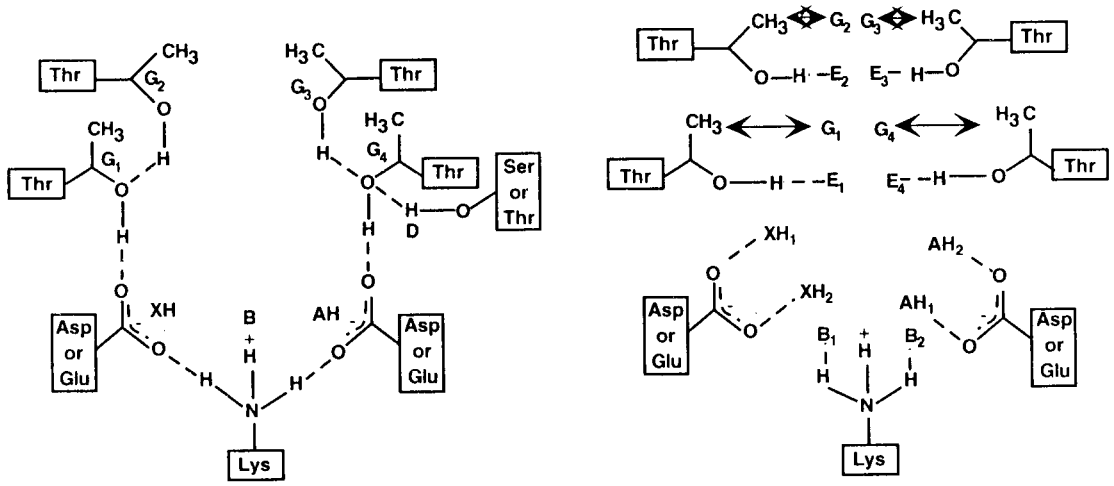


Fig. 4. Schematic representation (left) of the sweetness receptor in its resting state and (right) activated with sweetener through a 14 element interaction (after Tinti & Nofre, 1996).

*2.1.4. The α-helix receptor protein theory*

Another model for the sweet taste receptor has been introduced by Suami and Hough (1991) who postulate that the AH-B interaction of sweet molecules is at the N-terminus of a receptor protein which has a right-handed α-helical conformation. Certainly these ideas are consistent with the chiral specificity of the sweet taste response.

Although the SAR models listed above differ in their details, they all include an AH-B interaction and the modulation of hydrogen bonds as essential to the initiation transduction. Cloning the sweet receptor protein should yield the tools to observe the ligand binding reaction directly. Then it will be interesting to see what role the AH-B interaction plays in the reduction of the energy of the initial transition state of the sweet reaction.

## 3. Direct G-protein interaction (DGI)

Animal studies performed by Naim, Seifert, Nürnberg, Grünbaum and Schultz (1994) suggest that some taste substances are direct G-protein activators. Apparently, they can bypass the receptor step and interact directly with the G-proteins or other elements of the cascade further downstream. This mechanism of action is postulated for non-sugar sweeteners with amphiphilic properties that enable them to cross membranes through a process referred to as "electrophoretic transfer". Fig. 5 outlines the many implications of the recent research into primarily rodent taste systems.

Some recent results (Bernhardt et al., 1996; Lindemann, 1996) have suggested that the only second messenger formed during stimulation by non-sugar sweeteners is $IP_3$ and that sucrose causes the formation only of cAMP. These results suggest that direct G-protein activation is likely to co-exist with taste sensation initiated by putative taste receptors (SR and GR) located at the apical plasma membrane. This behavior is indistinguishable from the pharmacology of some drugs, for example the neuropeptide bradykinin.

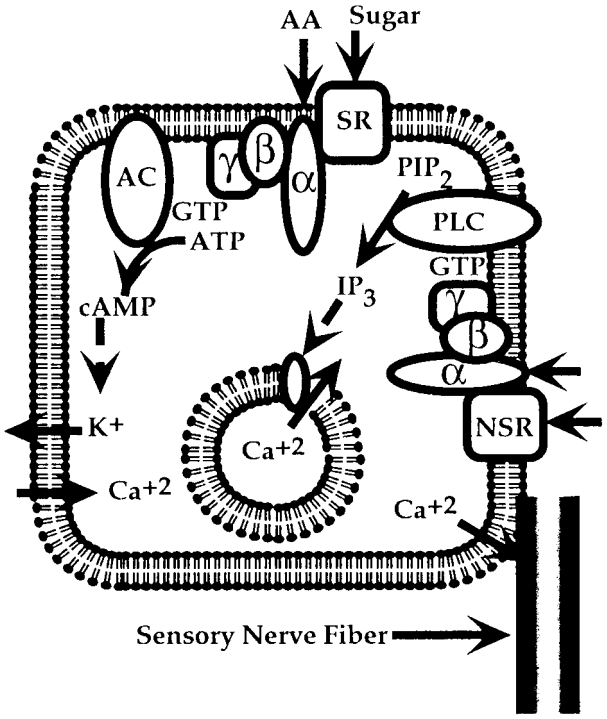


Fig. 5. A representation of some of the implications from recent research in mammalian taste transduction. The 7-transmembrane G-protein-mediated sugar taste receptor protein "SR" is activated only by sugars while amino acid-based sweeteners "AA" may act directly on the G-protein of the sugar receptor or on the G-protein of a non-sugar receptor "NSR" or at the 7-transmembrane protein of the NSR directly. α, β and γ are G-protein subunits; AC is adenylate cyclase; PLC is phospholipase C; $PIP_3$ is phosphatidylinositol biphosphate; $IP_3$ is inositol triphosphate (after Naim et al., 1996).

Bradykinin and kallidin apparently directly bind to G proteins activating phospholipase $A_2$ and phospholipase C. Kinin-induced phospholipase C activation leads to an increase in $IP_3$ and thus cytosolic $Ca^{2+}$ in exactly the same way saccharin increases in $IP_3$ and $Ca^{2+}$ when it binds directly to the G-protein in the rat circumvallate taste buds.

## 4. Conclusion

We can see that SR and GR receptors may have transduction mechanisms that involve similar initial chemistries, e.g. AH-B. It is difficult to envisage how the direct activation mechanism could use chemistries similar to those that evolved with the 7-transmembrane receptor proteins. However, if the human sweet taste response involves two or three different receptor mechanisms, then the complex multi-attachment theories will, in fact, yield a composite of all the different sweet receptor sites and their transduction mechanisms. Furthermore, several lines of evidence suggest that both sweet and bitter tastes are transduced via receptors coupled to heterotrimeric guanine-nucleotide binding proteins (G-proteins) (Kinnamon & Cummings 1992; Margolskee, 1993). These results suggest that both sweet and bitter reception share the same transduction components and that the non-sugar sweet receptor system is related to the bitter receptor system if it is not in fact the same. This would go a long way toward explaining the puzzling sweetness of α-mannose and the bitterness of its β-anomer.

After 30 years, the AH-B theory remains a possible explanation for the ligand binding chemistry that induces sweet taste response. However, the role, if any, of multiple receptors and multiple transduction mechanisms will eventually be clarified by the isolation of human sweet receptors(s), their structural determination and functional elucidation. Once the structural details of the receptor site and the ligand reaction are known, molecular dynamic simulations (Brady & Schmidt, 1993) of the initial chemistry of sweet taste will be possible. If our present interpretation of the facts is correct, at least two different sweet taste transduction systems will be revealed and the relationship between sweet and bitter taste explained.

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