Sugars in Nutrition, edited by M. Gracey,
N. Kretchmer, and E. Rossi,
Nestlé Nutrition Workshop Series, Vol. 25.
Nestec Ltd., Vevey/Raven Press, Ltd., New York © 1991.

Receptors and Transduction Mechanisms for Sweet Taste: An Overview

Susan S. Schiffman

Department of Psychology, Duke University, Durham, North Carolina 27706, USA

From the outset, it should be emphasized that no sweet receptor has ever been isolated, nor are the transduction mechanisms that induce sweet taste fully understood. Various molecules impart sweet taste in humans. These include monosaccharides, disaccharides, diterpene glycosides, polyols, amino acids, dipeptides, proteins, and other nonsugars. A feature common to most of these molecules is the capacity to form a pair of simultaneous hydrogen bonds with a putative receptor in the taste cell membrane. Shallenberger and Acree (1) hypothesized that sweet-tasting molecules possess an AH-B configuration, where A and B are electronegative atoms separated by 0.25 to 0.4 nm and H is a hydrogen atom that is part of a polarized system A-H. A complementary AH-B group is presumed to exist in the taste cell membrane that interacts with the AH-B group in the molecule to form two simultaneous hydrogen bonds. A third lipophilic binding site has been proposed for intense sweetness by Deutsch and Hansch (2) and by Kier (3).

Confirmation of the validity of the AH-B hypothesis has proven difficult, however, because the presence of an AH-B group does not guarantee that a molecule will taste sweet. The AH-B theory merely explains, after the fact, certain similar characteristics of molecules known to taste sweet but has little predictive value.

Our knowledge of the nature of the interaction of the sweet-tasting molecule with its receptor(s) derives from a range of disciplines, including biochemistry, electrophysiology, psychology, and biophysics. The topics to be addressed here are (a) biochemical approaches to understanding sweet receptors, (b) electrophysiological and behavioral approaches to understanding sweet receptors, (c) psychophysical approaches to understanding sweet receptors, and (d) psychophysical, electrophysiological, and transport studies to elucidate transduction mechanisms that mediate sweetness.

BIOCHEMICAL APPROACHES TO UNDERSTANDING SWEET RECEPTORS

The search for receptors that bind sweet-tasting molecules has not enjoyed the same degree of success as the search for receptors that bind hormones and neuro-

transmitters. There are two reasons for this. First, the affinity of most tastants, including sugar molecules, for receptors is low. Whereas the K_Ds for hormones may range from 10^{-11}M to 10^{-8}M, the K_D values for sugars may be as high as 0.5 M. Second, it has proven difficult to isolate taste cells from surrounding epithelium.

In spite of these limitations, there have been numerous biochemical studies aimed at elucidating the nature of sweet receptors. In the earliest studies, a protein fraction was isolated from bovine tongue epithelium that exhibited either ultraviolet difference spectral changes or refractive index changes in the presence of sugars or other sweet-tasting molecules (see ref. 4 for review). Similar preparations from tongues of rats and monkeys also displayed spectral changes in the presence of sweeteners (5). The sweetener concentrations found to be effective in these studies were approximately the same concentrations found to be effective in behavioral and neural studies. However, it is premature for several reasons to conclude that these particular protein fractions contain sweet receptors. First, the protein fraction that was derived from whole tongue epithelium was found to be contaminated wth sugar-metabolizing enzymes. Second, the protein fraction complexed wth nonsweet molecules, such as dimethyl sulfoxide (6).

Other studies have investigated binding of sugars both to taste papillae and to isolated lingual membranes. ^{14}C-labeled sugars were found to bind more to bovine fungiform and circumvallate papillae that contain taste buds than to filiform papillae that lack buds (7). Although the binding was weak (K_D from 10^{-1} to 10^{-3}M), it is in the same range as neurophysiological studies. [^{14}C]Glucose binding to plasma membrane fragments also has been reported in bovine circumvallate and fungiform papillae (8).

Immunological approaches have been used to investigate the nature of sweet receptors. Antibodies raised against thaumatin, a sweet-tasting plant protein, were found to crossreact with other sweet compounds, including sucrose, aspartame, calcium cyclamate, and monellin (9). The immunoreactivity and differential sweet taste of these sweeteners were found to be highly correlated, which led the authors to suggest that the structural feature of the antigenic determinant may be similar to that of the sweet receptor.

ELECTROPHYSIOLOGICAL AND BEHAVIORAL APPROACHES TO UNDERSTANDING SWEET RECEPTORS

Electrophysiological and behavioral data from animals are consistent with the biochemical findings. Neurophysiological studies have found that the affinity of sugars for taste receptors is weak (10,11). Electrophysiological studies, like biochemical studies, suggest that sweet receptors are proteins because proteolytic enzymes can suppress the neural responses to sweet stimuli (12). Both Pronase E and semialkaline protease suppressed the sweet responses of sugars, such as sucrose, glucose, and fructose, with no effect on salty, bitter, or sour stimuli. The proteolytic enzymes

also suppressed sweet responses to saccharin, glycine, and DL-alanine, which suggests that receptors for sweet-tasting nonsugars also are mediated by a protein.

Compounds known as "taste modifiers" can selectively suppress or induce sweet taste responses. Extracts from leaves of the Chinese jujuba tree *Ziziphus jujuba* and the Indian plant *Gymnema sylvestre* (13,14) suppress sweet responses. A protein from berries of the West African shrub *Synsepalum dulcificum* (miracle fruit) elicits a sweet taste from acids (15). The mechanism by which these taste modifiers act is not known.

Although proteolytic enzymes and taste modifiers can globally affect most sweet-tasting molecules, evidence from animal studies suggests that there is a multiplicity of sweet receptor types. The first line of evidence is that there are extensive species differences in the responses to sweet-tasting molecules (16,17). For example, the new world monkey *Saguinus midas tamarin* responds to the intense sweet proteins monellin and thaumatin, whereas rats and guinea pigs do not (18). Squirrel monkeys reject saccharin, whereas rats prefer it (19). Within rodents, the gerbil is responsive to more sweeteners than is the rat (20). What is constant, however, are responses to sugars. All of these species perceive sugars as sweet.

A second line of evidence for multiple sweet receptor types derives from response spectra of individual taste fibers of the chorda tympani nerve. Faurion et al. (21,22) found that individual neurons had unique response patterns to sweeteners. For example, whereas one neuron responded strongly to one sweetener and less to a second, another neuron may have an opposite pattern. A third argument for multiple sweet receptor sites is the finding that alloxan selectively depresses neural activity to sugars but does not reduce responses to sodium saccharin in rat (23).

The conclusion to be drawn from these animal studies is that there are multiple sweet receptor types, each with multiple sensitivities that are tuned to respond to more than one sweetener. Thus, it is probable that sucrose binds to several types of sweet receptors, and for this reason, a single geometric shape for a sucrose receptor is too restrictive to describe the sucrose–receptor interaction.

PSYCHOPHYSICAL APPROACHES TO UNDERSTANDING SWEET RECEPTORS

Psychophysical studies in humans are consistent with biochemical, electrophysiological, and animal behavioral studies. Cross-adaptation studies further confirm that there are multiple sweet receptors, and multidimensional analysis suggests that sweetness itself is a multidimensional quality.

Sweetness Is Mediated by Multiple Receptor Sites

Several lines of evidence from psychophysical studies in humans lead to the conclusion that sweetness is mediated by multiple receptor mechanisms. The first line of evidence from human psychophysics for multiple sweet receptors derives from

TABLE 1. *Cross-adaptation of sweeteners*[a]

	Adapting solution							
	Acesulfame-K	Aspartame	Ca cyclamate	Glucose	Neohesperidin dihydrochalcone	Na saccharin	D-Tryptophan	Xylitol
Test solution								
Acesulfame-K		17.0	20.2	8.4	−9.6	55.6	33.2	34.8
Aspartame	11.4		4.8	16.8	−6.4	−1.2	42.6	33.4
Ca cyclamate	−3.6	7.7		23.6	23.6	16.0	−5.6	15.8
Glucose	−4.6	−2.3	21.3		2.4	−5.6	8.6	24.8
Neohesperidin dihydrochalcone	−4.1	13.6	6.5	3.8		−9.8	18.4	11.3
Na saccharin	37.1	9.2	−3.2	19.4	−5.3		12.8	11.6
D-Tryptophan	−6.2	43.0	−1.8	30.8	3.2	6.2		31.6
Xylitol	−1.8	5.6	21.4	13.5	−10.4	8.1	12.4	

From Schiffman SS, et al. (24).

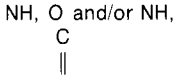
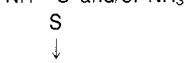
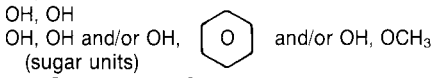
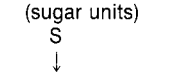
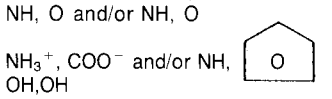
[a] A positive value represents a decrement in perceived sweetness. A negative value reflects an enhancement.

cross-adaptation studies (24). When prolonged exposure or adaptation to one sweetener results in decreased response to another, it is assumed that the two sweeteners share common receptor sites. Alternatively, if adaptation to a given sweetener does not lead to a reduced response from another sweetener, the implication is that different receptors mediate the perception of these two sweeteners.

In one cross-adaptation study (24), subjects first tasted a sweet solution *A* and rated its intensity. Next, they held a different sweet solution *B* in their mouths until the sweet taste disappeared. Finally, they tasted solution *A* again to reestimate its sweetness after adaptation with *B*. Table 1 shows the results of the cross-adaptation of eight sweeteners with one another. A positive value represents a decrement in perceived sweetness, and a negative value reflects an enhancement. Examination of the values in any one column shows that both enhancement and reduction in sweetness occur after adaptation to a given sweetener. This finding is not compatible with the existence of a single sweet receptor type. A similar conclusion must be drawn from the finding that cross-adaptation between two sweeteners is not reciprocal. For example, adaptation with calcium cyclamate blunted the sweetness of acesulfame-K, but adaptation with acesulfame-K enhanced the intensity of calcium cyclamate. This suggests that these two sweeteners are not binding to identical receptors.

Several other conclusions can be drawn from Table 1. When a sugar (glucose) was the adapting solution, a reduction in sweetness was found for all the other sweeteners. This suggests that sugars may bind to the greatest number of receptor types, whereas artificial sweeteners, such as acesulfame-K may interact with a more limited number. The results in Table 1 also suggest that molecules with similar or identical AH-B systems cross-adapt most strongly (see Table 2 for possible AH-B systems).

TABLE 2. *Possible AH = B systems for sweeteners in Table 1*

Stimulus	Number	Type[a]
Acesulfame-K[b]	2	
Aspartame	2	
Ca cyclamate	1	
Glucose	1	OH, OH
Neohesperidin dihydrochalcone	3	
Saccharin (sodium salt)[b]	2	
D-Tryptophan	2	
Xylitol	1	OH,OH

From Schiffman SS, et al. (24).

[a] S→O refers to the fact that S is an electron-donating atom. It does not form a true covalent bond with the O but donates electrons, making the O electronegative and indicating that it has an unshared pair of electrons (Ö).

[b] Strictly speaking, the N in acesulfame-K and sodium saccharin should be N^- because it is the salt form (Na^+ for saccharin, K^+ for acesulfame-K) that is normally tasted. However, the "nonsalt" form (NH) is also sweet.

For example, acesulfame-K and Na saccharin have identical possible AH-B systems and mutually cross-adapt.

The second line of psychophysical evidence for multiple receptor sites is the nonhomogeneous variability in the perception of sweeteners by individual subjects for thresholds, intensity ratings, and the effect of Pronase E. When threshold values for a range of sweeteners were compared, it was found that for a given subject, it was impossible to predict the threshold of one sweetener given the threshold of another (21,25). This finding suggests that there are multiple receptor sites for sweeteners and that their relative numbers are unique for each individual. Interindividual variability also occurs for intensity ratings of suprathreshold concentrations (21,25) and relative reduction in sweetness by Pronase E in humans (21). These results would be impossible to interpret if there were a single sweet receptor type.

The Multidimensional Taste Quality of Sweetness

Traditional views of taste have presumed that there are only four taste qualities: sweet, sour, salty, and bitter. All other taste sensations were presumed to be mixtures

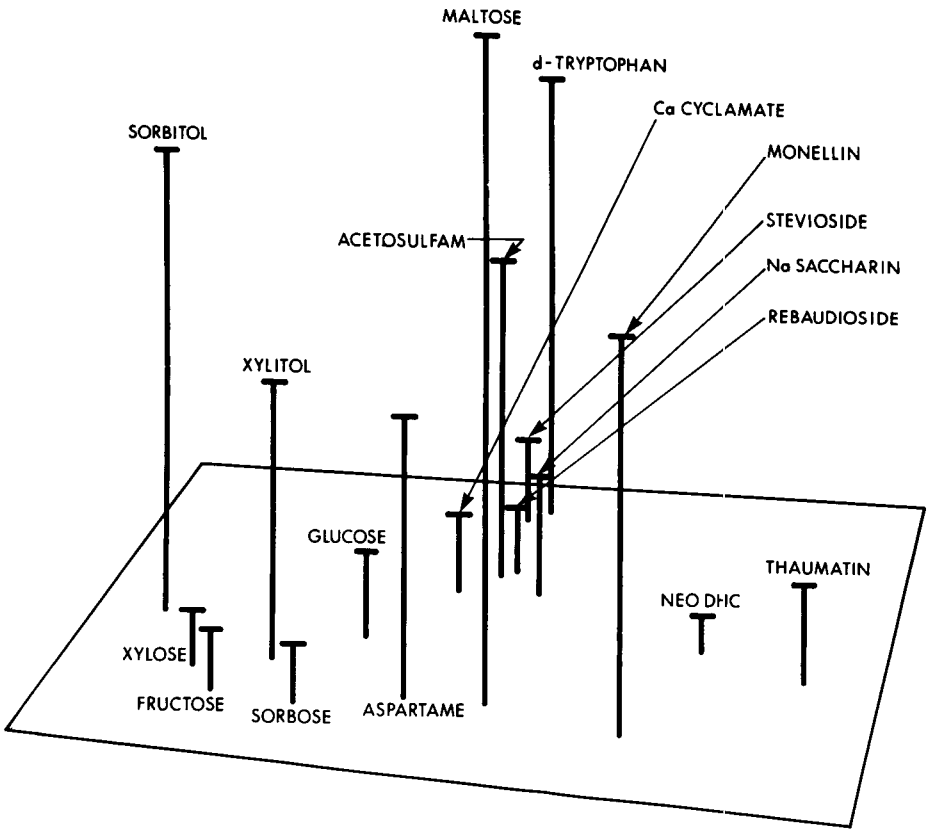


FIG. 1. Three-dimensional solution achieved by multidimensional scaling of similarity judgments among 17 sweeteners. Sweeteners judged to be similar in quality are arranged close to one another in the three-dimensional map. Sweeteners judged to be different from one another are distant from one another in the map. From Schiffman SS, et al. (27).

of these four. However, psychophysical data obtained without adjective labels suggest not only that the qualitative range of taste is broader than the four so-called primary tastes (26) but that sweetness itself is not a unitary quality (27).

In one experiment, a computer-based mathematical technique called multidimensional scaling (MDS) was applied to ratings of similarity among 17 sweeteners that ranged widely in chemical structure (27). MDS arranged sweeteners judged similar in taste quality so that they were close to each other in a spatial map. Sweeteners perceived as most different from one another were positioned far from one another in the map. The three-dimensional solution achieved by MDS for the 17 sweeteners is shown in Fig. 1. The tops of the posts in this figure represent the position of each sweetener in the three-dimensional space.

The arrangement of the space based on similarity of taste reveals the following. Monosaccharides, including fructose, glucose, sorbose, and xylose, are located close

to one another, with polyhydric alcohols, xylitol, and sorbitol close by. The three sweeteners with long aftertastes, monellin, thaumatin, and neohesperidin dihydrochalcone, are located toward the right and separate from the sugars. Sweeteners with bitter or metallic tastes, including acesulfame-K, rebaudioside, stevioside, sodium saccharin, and D-tryptophan tended to group. Calcium cyclamate was positioned between the sweet-bitter stimuli and the sugars. Maltose was located between the sugars and the sweeteners with lingering aftertastes.

The experimental subjects in this experiment continued to comment that although each sweetener had unique side tastes and temporal properties, the nature of the sweetness itself differed among the sweeteners. This suggests that sweetness is not a single or unitary quality but rather should be viewed as multidimensional. This multidimensional character of sweetness also suggests the existence of multiple sweet receptor types.

Psychophysical Data Correlate with Number of AH-B Systems

A relationship between detection thresholds and hydrogen bonding has been reported that supports Shallenberger and Acree's AH-B hypothesis. Schiffman et al. (25) measured the detection and recognition thresholds for 11 sweeteners that varied in chemical structure. The mean detection thresholds for 12 young subjects (mean age 21.6 years) for the sweeteners were ranked from lowest to highest. A strong inverse relationship was found between the magnitude of the detection thresholds and the number of possible types of systems for hydrogen bonding (i.e., AH-B systems). Sweeteners with the lowest thresholds have many possible AH-B systems (e.g., thaumatin) and are thus capable of concerted intermolecular hydrogen bonding. Sweeteners with the highest thresholds have only one type of AH-B system. Recognition thresholds followed the same pattern but were 3.54 times higher on average than detection thresholds.

STUDIES TO ELUCIDATE TRANSDUCTION MECHANISMS THAT MEDIATE SWEETNESS

Sweet taste sensations are mediated not only by multiple receptor types but also by a multiplicity of transduction mechanisms that vary with the species. Na^+ transport, K^+ transport, and cAMP production all have been implicated in the transduction mechanism for sweet taste.

Na^+ Transport Pathways

An early step in both salt and sweet taste transduction in some species is the entry of sodium ions into taste receptor cells. This was first discovered by DeSimone et al. (28,29) and Schiffman et al. (30), who found that application of the pharmaco-

logical probe amiloride to the tongue blocked responses to NaCl and sweeteners. Amiloride is a sodium transport inhibitor that blocks the passive diffusion of Na^+ through apical plasma membranes in a variety of transporting epithelia.

Na^+ channels play a role in salt and sweet taste transduction in humans (30). When amiloride was applied to small areas of the dorsal surface of the tongue in human psychophysical experiments, it reduced the perceived intensity of NaCl (0.2–0.6 M) by 50 to 65% and of sweeteners by an average of 59.1% (Fig. 2). It did not reduce the perceived intensities of potassium or calcium salts, acids, or bitter compounds. Extracellular recordings from first-order or second-order taste neurons in rats, gerbils, and dogs have confirmed the human findings that amiloride reduces taste responses to NaCl (see ref. 31 for review.) However, these electrophysiological studies have found species differences in the effectiveness of amiloride to block sweet taste responses; that is, it reduces the magnitude of sweet responses in dogs but has no effect in rodents.

The human and electrophysiological findings are consistent with transport studies of isolated lingual epithelium placed in an Ussing chamber. NaCl and saccharides induce a mucosal to serosal amiloride-sensitive transepithelial current in the dorsal lingual epithelium of dogs (29) and rabbits (32). The stimulation of current by sugars and NaCl is abolished by the Na,K-ATPase inhibitor ouabain (33,34). This suggests that transcellular currents mediate sweet and salty tastes, with Na^+ entering the cell on the apical side via amiloride-inhibitable pathways and exiting on the serosal side through ouabain-inhibitable Na^+,K^+-ATPase.

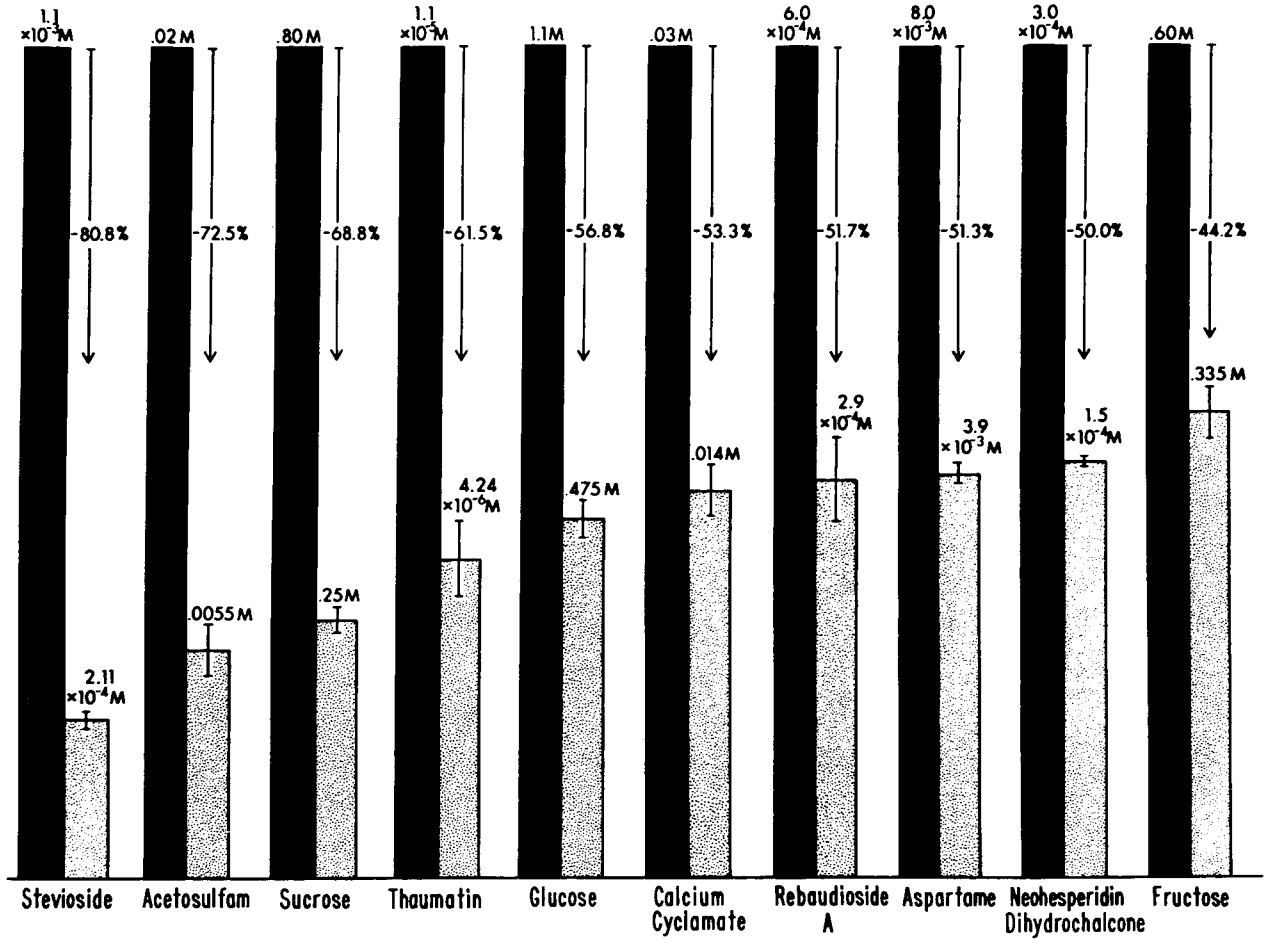
Recent evidence suggests that the amiloride-inhibitable entry pathway stimulated by sugars in dogs (34) not only transports Na^+ but also can transport other ions, such as K^+, Rb^+, and Cs^+, as well. A variety of amiloride-sensitive epithelial channels have been identified in other tissues (35). Thus, the amiloride-inhibitable pathway that mediates sweet taste in dogs may not be identical to the one that is responsible for salty taste. The sweet receptor for saccharides in dogs appears to be associated directly with the amiloride-sensitive pathway because pharmacological agents that mimic or modify the intracellular messengers cAMP, cGMP, or Ca^{2+} have no effect on saccharide-stimulated transport.

cAMP and K^+ Transport

There clearly are species-specific differences in the type of transduction mechanisms that mediate sweetness. Although amiloride-sensitive channels are intricately involved in transducing sweet taste in humans and dogs, they appear to play no role

FIG. 2. Amiloride blocks the taste of sweeteners in humans. The concentration of the standard stimulus applied to the tongue in the presence of amiloride is represented by the black bar. The stippled bar represents the mean concentration that matched the mean perceived taste intensity of the standard for 10 subjects. The standard error and percent inhibition are given as well. From Schiffman SS, et al. (30).

SWEETENERS


1.1 ×10⁻³M
-80.8%
2.11 ×10⁻⁴M
Stevioside
.02 M
-72.5%
.0055 M
Acetosulfam
.80 M
-68.8%
.25M
Sucrose
1.1 ×10⁻⁵M
-61.5%
4.24 ×10⁻⁶M
Thaumatin
1.1M
-56.8%
.475 M
Glucose
.03M
-53.3%
.014M
Calcium Cyclamate
6.0 ×10⁻⁴M
-51.7%
2.9 ×10⁻⁴M
Rebaudioside A
8.0 ×10⁻³M
-51.3%
3.9 ×10⁻³M
Aspartame
3.0 ×10⁻⁴M
-50.0%
1.5 ×10⁻⁴M
Neohesperidin Dihydrochalcone
.60M
-44.2%
.335 M
Fructose

in rodents. The type of transduction mechanism invoked by a given sweetener within a single species also is dependent on its chemical structure. In humans, for example, modification of intracellular cAMP levels alters the perceived sweetness of some compounds but has no effect on others. In one experiment, cAMP levels within a taste cell were modified by adaptation of the anterior tongue with 10 μM caffeine (36). Caffeine is a methyl xanthine, which is known to antagonize adenosine receptors and thereby modulate adenylate cyclase and subsequent cAMP formation within a cell. Caffeine enhanced the taste of artificial sweeteners thaumatin, stevioside, sodium saccharin, acesulfame-K, neohesperidin dihydrochalcone, and D-tryptophan. However, it had no effect on sucrose or fructose, which suggests that the transduction mechanism for sugars may be different from that for the artificial sweeteners in humans.

K^+ currents also may be involved in sweet taste perception, although this has not yet been shown conclusively to be the case. Intracellular application of cAMP can depolarize taste cell membranes by deactivation of K^+ channels (37,38). Sucrose has been reported to activate a GTP-dependent adenylate cyclase in rat (39), which presumably modifies cAMP levels and could in turn inactivate K^+ channels.

CONCLUSION

Multiple receptors and transduction mechanisms are involved in the perception of sweet taste. Sugars bind to a wider population of receptors than do artificial sweeteners and exhibit different modes of transduction. An amiloride-inhibitable pathway mediates sweet taste in humans.

REFERENCES

1. Shallenberger RS, Acree TE. Chemical structure of compounds and their sweet and bitter taste. In: Beidler LM, ed. *Handbook of sensory physiology*, vol 4. Berlin, New York: Springer-Verlag, 1971:221–77.
2. Deutsch EW, Hansch C. Dependence of relative sweetness on hydrophobic bonding. *Nature* 1966; 211:75.
3. Kier LB. A molecular theory of sweet taste. *J Pharm Sci* 1972;61:1394–7.
4. Price S, DeSimone JA. Models of taste receptor cell stimulation. *Chem Senses* 1977;2:427–56.
5. Hiji Y, Kobayashi N, Sato M. Sweet-sensitive protein from the rat tongue: its interaction with various sugars. *Comp Biochem Physiol [B]* 1971;39B:367–75.
6. Nofre C, Sabadie J. A propos de la proteine linguale dite "sensible aux sucres." *CR Seances Acad Sci Ser [D]* 1972;274:2913–5.
7. Cagan RH. Biochemical studies of taste sensation. 1. Binding of ^{14}C-labeled sugars to bovine taste papillae. *Biochim Biophys Acta* 1971;252:199–206.
8. Ostretsova IB, Safarian EK, Etingof RN. On the presence and localization of glucose-binding proteins in the tongue. *Dokl Akad Nauk SSSR* 1975;223:1484–7.
9. Hough CAM, Edwardson JA. Antibodies to thaumatin as a model of the sweet taste receptor. *Nature* 1978;271:381–3.
10. Beidler LM. Taste receptor stimulation. *Prog Biophys* 1962;12:109–51.
11. Pfaffmann C. Taste, its sensory and motivating properties. *Am Sci* 1964;52:187–206.
12. Hiji Y. Selective elimination of taste responses to sugars by proteolytic enzymes. *Nature* 1975; 256:427–9.

13. Yackzan KS. Biological effects of *Gymnema sylvestre* fractions. II. Electrophysiology—effect of gymnemic acid on taste receptor response. *Ala J Med Sci* 1969;6:555–63.
14. Kennedy LM, Halpern BP. A biphasic model for action of the gymnemic acids and ziziphins on taste receptor cell membranes. *Chem Senses* 1980;5:149–58.
15. Brouwer JN, Glaser D, Hard AF, et al. The sweetness-inducing effect of miraculin: behavioral and neurophysiological experiments in the rhesus monkey *Macaca mulatta*. *J Physiol (Lond)* 1983; 337:221–40.
16. Naim M, Rogatka H, Yamamoto T, Zehavi U. Taste responses to neophesperidin dihydrochalcone in rats and baboon monkeys. *Physiol Behav* 1982;28:979–86.
17. Sato M, Hiji Y, Ito H. Taste discrimination in monkey. In: LeMagnen J, Macleod P, eds. *Olfaction and taste*, vol 4. London: IRL, 1977:233–40.
18. Brouwer JN, Hellekant G, Kasahara Y, van der Wel H, Zotterman Y. Electrophysiological study of the gustatory effects of the sweet proteins monellin and thaumatin in monkey, guinea pig and rat. *Acta Physiol Scand* 1973;89:550–7.
19. Fisher GL, Pfaffmann C, Brown E. Dulcin and saccharin taste in squirrel monkeys, rats, and men. *Science* 1965;150:506–7.
20. Jakinovich W, Jr. Stimulation of the gerbil's gustatory receptors by artificial sweeteners. *Brain Res* 1981;219:69–81.
21. Faurion A, Saito S, MacLeod P. Sweet taste involves several distinct receptor mechanisms. *Chem Senses* 1980;5:107–21.
22. Faurion A, MacLeod P. Sweet taste receptor mechanisms. In: Birch GG, Parker KJ, eds. *Nutritive sweeteners*. London: Applied Science Publishers, 1982;247–73.
23. Zawalich WS. Depression of gustatory sweet response by alloxan. *Comp Biochem Physiol [A]* 1973; 44:903–9.
24. Schiffman SS, Cahn H, Lindley MG. Multiple receptor sites mediate sweetness: evidence from cross adaptation. *Pharmacol Biochem Behav* 1981;15:377–88.
25. Schiffman SS, Lindley MG, Clark TB, Makino C. Molecular mechanism of sweet taste: relationship of hydrogen bonding to taste sensitivity for both young and elderly. *Neurobiol Aging*, 1981;2:173–85.
26. Schiffman SS, Erickson RP. The issue of primary tastes versus a taste continuum. *Neurosci Biobehav Rev* 1980;4:109–17.
27. Schiffman SS, Reilly DA, Clark TB. Qualitative differences among sweeteners. *Physiol Behav* 1979; 23:1–9.
28. DeSimone JA, Heck GL, DeSimone SK. Active ion transport in dog tongue: a possible role in taste. *Science* 1981;214:1039–41.
29. DeSimone JA, Heck GL, Mierson S, DeSimone SK. The active ion transport properties of canine lingual epithelia in vitro: implications for gustatory transduction. *J Gen Physiol* 1984;83:633–56.
30. Schiffman SS, Lockhead E, Maes FW. Amiloride reduces the taste intensity of Na^+ and Li^+ salts and sweeteners. *Proc Natl Acad Sci USA* 1983;80:6136–40.
31. Schiffman SS. The role of sodium and potassium transport pathways in taste transduction: an overview. *Chem Senses* 1990;15:129–35.
32. Simon SA, Robb R, Garvin JL. Epithelial responses of rabbit tongues and their involvement in taste transduction. *Am J Physiol* 1986;251:R598–R608.
33. Mierson S, DeSimone SK, Heck GL, DeSimone JA. Sugar-activated ion transport in canine lingual epithelium. *J Gen Physiol* 1988;92:87–111.
34. Simon SA, Labarca P, Robb R. Activation by saccharides of a cation-selective pathway on canine lingual epithelium. *Am J Physiol* 1989;256:R394–R402.
35. Garty H, Benos DJ. Characteristics and regulatory mechanisms of the amiloride-blockable Na^+ channel. *Physiol Rev* 1988;68:309–73.
36. Schiffman SS, Gill JM, Diaz C. Caffeine intensifies taste of certain sweeteners: role of adenosine receptor. *Pharmacol Biochem Behav* 1986;22:195–203.
37. Avenet P, Hofmann F, Lindemann B. Transduction in taste receptor cells requires cAMP-dependent protein kinase. *Nature* 1988;331:351–4.
38. Tonosaki K, Funakoshi M. Cyclic nucleotides may mediate taste transduction. *Nature* 1988;331: 354–6.
39. Lancet D, Striem BJ, Pace U, Zehavi U, Naim M. Adenylate cyclase and GTP binding protein in rat sweet taste transduction. *Soc Neurosci Abstr* 1987;13:361.

DISCUSSION

Dr. Wahlqvist: These findings have significant implications for product development with nonnutritive sweeteners because much of the emphasis has been on low-energy, nonfat-containing products.

Dr. Schiffman: Several studies show that if the fat content of a diet is diluted but the sensory properties are kept constant, people will reduce their caloric intake and lose weight.

Dr. Rossi: What is your experience with sucrose and hyperactivity in children?

Dr. Schiffman: Sucrose does affect the sympathetic nervous system. However, double-blind studies have not found that sucrose leads to hyperactivity in children.

Dr. Lentze: I would like to ask why evolution has put lactose into the milk because it does not seem to be really necessary. Is it because of the taste, or is it because energy intake is driven by taste? Also, has nature put nucleotides into human milk as a taste enhancer?

Dr. Schiffman: All I can say is that people select foods on the basis of taste.

Dr. Kretchmer: There are animals that do not have lactose in their milk. The Pacific pinnipedia, for example, have no sugar whatsoever in their milk. So I don't know why lactose is in milk. There are milks that do not have lactose or, put another way, that do not have carbohydrate as a source of energy. Instead of sugar, it is replaced by fat. Sea lion milk or caribou milk contains almost 35% fat and no carbohydrate whatsoever. Sea lions make glucose from the glycerol of fat.

Dr. Guesry: A small comment answering Michael Lentze's question why there are nucleotides in human milk. More than 10 years ago, we investigated the effect of nucleotides in infant formulae on taste and consumption; the result was negative.

Dr. Schiffman: Nucleotides, such as IMP or GMP, do not potentiate taste significantly until concentrations near 1 mM.

Dr. Truswell: The question why the main sugar in most milks is lactose is fascinating. Lactose is rare in other foods except milk. In Australian marsupials, the milk contains not lactose but oligosaccharides of galactose. Why do they have that? Is it because there is galactose in the cerebral lipids?

Dr. Kretchmer: We thought the same thing but found that California sea lions make galactose very easily from glycerol through glucose.

Dr. Truswell: I think they have fat instead of lactose because they have to grow so much faster than other animals.

Dr. Kretchmer: The data I have seen from Messer and others show that Australian marsupials have conjugated lactosides in their milk. I do not understand why.

Dr. Guesry: There is no human milk without lactose, but up to 25% of American babies are receiving soya formula without lactose. There is no difference in the consumption of these substitutes versus other substitutes made with lactose.

Dr. Shafrir: In diabetes there is a loss of taste. My question is: is it due to the loss of taste receptors, or is it neuropathy involving reduced nerve conduction velocity, and can this be restored by insulin treatment?

Dr. Schiffman: That is a really good question. The sense of sweet taste seems to be less intense for people with diabetes. Whether it has to do with the peripheral neuropathy or the number of receptors is unclear. In treated diabetes, the taste thresholds come back to relatively normal levels.

Dr. Shafrir: Is the loss of feeling of heat and cold related to the same mechanism?

Dr. Schiffman: That suggests a peripheral neuropathy rather than the number of receptors on the tongue.

Dr. Lentze: I was interested that 10% or even 20% of patients on captopril lose their taste. What is the mechanism?

Dr. Schiffman: It is sulfhydryl bonding. There are many drugs affecting the sense of taste by that mechanism.