Taste processing: **Whetting our appetites**

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Two G-protein-coupled receptors have been identified that are present in the apical membranes of rat and mouse taste cells and differentially distributed across the tongue and palate. They are strong candidates for being taste receptors and their discovery has provided new tools for research into gustatory processing.

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Current Biology 1999, 9:R453–R455
http://biomednet.com/elecref/09609822009R0453

The sense of taste provides information important for ingestion of nutrients and avoidance of toxins. Specific classes of chemicals are associated with particular taste sensations: for example, sweetness is associated with sugars and other carbohydrates, and saltiness with sodium chloride. Ingestion of these substances serves to regulate energy and mineral balance. Bitter-tasting alkaloids or spoiled foods, which may have a sour taste, are rejected. Unlike vision and audition, no single stimulus continuum underlies taste; consequently, a diversity of mechanisms is responsible for transducing chemical cues into neural activity. These transduction mechanisms range from amiloride-sensitive ion channels, through which Na^+ ions may directly depolarize taste receptor cells, to several types of K^+ channel, which are blocked by H^+ ions or polyunsaturated fatty acids, to G-protein-coupled receptors, which are thought to underlie transduction of the tastes evoked by sweet and bitter compounds and also amino acids. The existence of G-protein-coupled receptors that serve as taste receptors has been inferred from biochemical studies [1], but not directly demonstrated.

In this context, it is exciting to see the recent cloning of two putative taste receptor proteins, TR1 and TR2 [2]. Using subtractive and differential screening techniques, mRNAs encoding two novel G-protein-coupled receptors were identified that are expressed in taste bud cells, but not in other chemosensory epithelia (olfactory or vomeronasal) or in the brain. The expression does not seem to be restricted solely to taste tissue, however, as TR1 is also expressed in testes. TR1 and TR2 are related to the subfamily of G-protein-coupled receptors that have very long amino-terminal extracellular domains, thought to be the ligand-binding domains. This subfamily includes metabotropic glutamate receptors, Ca^{2+}-sensing receptors and putative pheromone receptors of mouse and some fish species. Moreover, TR1 and TR2 are differentially expressed in taste buds of the anterior tongue, posterior tongue and palate of rats and mice, suggesting that they could be at least partly responsible for the differences in gustatory sensitivities among these taste bud populations.

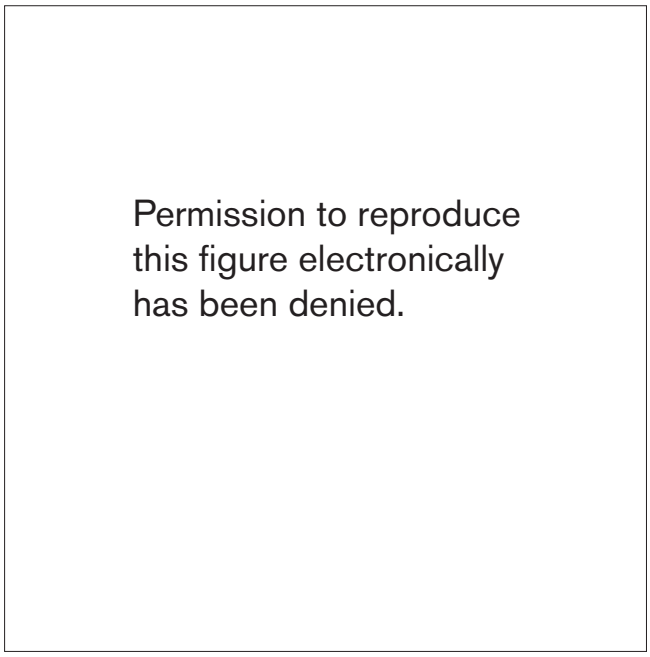
A fundamental question in taste is how chemicals with diverse structures evoke taste sensations — saltiness, sweetness, sourness or bitterness. Underlying this question is the assumption that these human sensations are applicable to species that are the subject of biological investigation and the belief that all species respond similarly to sapid chemicals (those having taste). Both of these assumptions are questionable. Nevertheless, there has been a universal attempt to relate biological data at all levels to human taste sensation. Certainly, many stimuli that are perceived as having a similar taste by humans are also treated similarly by animals, but species differences in taste are well documented. Thus, drawing a direct correspondence between animal data and human sensation can be misleading.

Furthermore, there is not a strict correspondence between human taste quality and chemical class. For example, many carbohydrates are sweet, but others are not. Furthermore, other compounds, such as weak sodium chloride solutions, lead acetate and chloroform, also impart a sweet taste. Most salts evoke multiple perceptions in humans, which can include saltiness, sourness, sweetness or bitterness. Thus, caution should be exercised in describing receptor proteins isolated from animal tissue as ‘sweet’ or ‘bitter’ receptors, even in the face of direct evidence that these proteins are involved in the transduction of sucrose or quinine. For example, does the bitterness of calcium salts arise from the same transduction cascade as that of quinine or denatonium? Probably not, but the answer to such a question is one of the goals in understanding gustatory neural coding.

Biophysical studies of taste transduction have suggested that both sweet-tasting and bitter-tasting stimuli are transduced by G-protein-coupled receptors [3]. A G-protein subunit, α-gustducin, which is highly similar in structure to rod transducin, is expressed in rat taste tissue [4]. Behavioral experiments on gustducin knockout mice have shown that these mutant animals do not exhibit the normal preference or aversion commonly seen in response to compounds described as sweet or bitter [5]; they also exhibit decreased electrophysiological responses in peripheral gustatory neural recordings.

A quantitative assessment in the rat has shown that those taste bud populations that are highly responsive to either

Figure 1



Mean responses of four groups of neurons (G1–G4) in the nucleus of the solitary tract (NST) of the rat to stimulation of the tongue with 0.5 M sucrose (S), 0.1 M NaCl (N), 0.01 M HCl (H), and 0.01 M quinine hydrochloride (Q). These cells receive the first synaptic input from the peripheral taste fibers and project rostrally to carry taste information to the forebrain through several additional synapses. Taste-responsive neurons are broadly tuned to stimuli with different tastes, as seen in this figure, and often respond to temperature changes and tactile stimulation. Thus, regardless of the specificity of transduction mechanisms or taste receptor cells, the coding of taste quality ultimately depends upon the activity of these and other broadly tuned central neurons. (Data modified with permission from [9].)

bitter or sweet stimuli — for example, vallate or palatal taste buds — have significantly more gustducin-expressing cells than the fungiform taste buds, which respond rather poorly to sweet and bitter stimuli [6]. Biochemical studies with bovine taste membranes have identified candidate receptor activities that respond to several bitter compounds by activating gustducin [1]. Taken together, these findings implicate gustducin in the transduction of both sweet-tasting and bitter-tasting compounds, although its exact role in these processes is still unclear [3]. Recent molecular studies have suggested that a metabotropic glutamate receptor variant may be involved in transducing the response to glutamate in rat taste receptors [7].

Understanding gustatory transduction is a first step in linking stimulus to perception. Between the receptor membrane and taste quality, however, lies a series of neural circuits that serve to process information about taste stimuli. The first element is the taste receptor cell. There are still only limited data on the sensitivity of individual receptor cells to gustatory stimuli, but several studies have suggested that a single taste cell transduces more than one kind of stimulus. The recent molecular data of Hoon *et al.* [2], demonstrating that some taste cells express both TR1 and TR2 and that neither of these putative receptors is uniformly co-localized with α-gustducin, are consistent with these observations. The profound deficit in the response to bitter and sweet stimuli exibited by gustducin knockout mice [5], combined with this lack of co-localization, strongly suggests that additional G-protein-coupled receptors must exist in taste cells.

Even if individual receptor cells respond to only a single stimulus, recordings from single peripheral taste axons have shown that these neurons — the second neural element in the pathway — respond to several different stimuli [8]. Although peripheral taste axons in mammals can be grouped according to their 'best' stimulus, such as sucrose-best and NaCl-best, these cells are broadly tuned across stimulus classes. Furthermore, as these peripheral fibers converge onto cells in the brain, central neurons become even more broadly tuned. The mean response profiles of four classes of neurons in the rat medullary taste area known as the 'nucleus of the solitary tract' to sucrose (S), NaCl (N), HCl (H) and quinine (Q) are shown in Figure 1. These neurons were classified by a hierarchical cluster analysis of their response profiles to a wide array of gustatory stimuli [9]. None of these neuron groups is specifically tuned to any one stimulus, each of which gives rise to neural activity in all of the groups and each of which is perceptually distinct to rats. This broad tuning is characteristic of neurons at all levels of the mammalian gustatory system.

There has been a great deal of controversy over the mechanisms of gustatory neural coding, primarily over whether particular groups of neurons comprise 'labeled lines' for taste quality, or whether taste quality is represented by the pattern of activity across broadly tuned cells, as in color vision (see [8]). Because gustatory neurons are broadly tuned to different classes of taste stimuli (Figure 1) and often respond also to changes in temperature and to tactile stimuli, the representation of taste quality is most likely accomplished by a pattern code.

The possible role of a chemotopic neural map as a representative of taste quality has been entertained over the years, but there is little compelling evidence to support the existence of such a map, except for the rather crude differences that exist in rodents in the gustatory sensitivities of different cranial nerves. For example, in the rat the palate is highly sensitive to salts and sweet stimuli, the posterior tongue to bitter and sweet stimuli, and the anterior tongue to salts and acids. Such marked differences in sensitivity do not exist for humans, despite the often cited but misleading 'tongue map' showing regional differences across the human tongue. Gustatory psychophysicists have known for many years that these

human tongue maps are wrong and that they arose earlier in this century as the result of misinterpretation of work reported in the 1800s (see [10]). It has, however, proved next to impossible to rid the secondary literature of these misrepresentations. In reality, although there are slight differences in threshold in different regions of the oral cavity, all qualities of taste can be elicited from all areas containing taste buds [11].

In their important paper on putative taste receptor proteins, Hoon *et al.* [2] argue that TR1 and TR2 may represent 'sweet' and 'bitter' receptors, respectively, because of their regional distribution. That is, TR1 is expressed equally heavily in fungiform and palatal taste buds and considerably less strongly in foliate and especially vallate taste buds. In contrast, TR2 is expressed heavily in vallate and foliate taste buds, much less strongly in palatal taste buds, and hardly at all in fungiform taste buds. However, rat fungiform taste buds are not very responsive to sweet stimuli, especially in comparison to the palate. Furthermore, the rat's glossopharyngeal nerve, which innervates the vallate and foliate taste buds, is more sensitive than its chorda tympani nerve to sweet stimuli [8]. So the equal distribution of TR1 in fungiform and palatal taste buds and its relative lack of expression in vallate and foliate buds does not correlate with the rat's taste sensitivities. Furthermore, as mouse and rat data were combined in this analysis (see Table 1 in [2]), and as there are large strain differences among mice in the sensitivities of their fungiform papillae [12], interpretation of these data in terms of perception is premature.

We now understand a great deal about how taste information is represented in the activity of central gustatory neurons. The transduction mechanisms used by the taste receptors and their connectivity with neurons at various levels of the central gustatory pathway are important pieces of information for our understanding of this system. For example, it has been shown that input to the brain from receptors employing amiloride-sensitive Na^+ channels is restricted to NaCl-best chorda tympani nerve fibers and central taste neurons [9]. Behavioral studies in rats have shown that amiloride treatment disrupts gustatory discrimination between sodium and non-sodium salts. We therefore know how this specific transduction mechanism relates to both central neural activity and behavior. The hope is that TR1 and TR2 are the first examples of what will become a larger group of putative taste receptors. Having these new molecular tools, and the potential to link them to specific classes of gustatory stimuli, will be extremely useful in helping us to understand the connectivity underlying neural coding in this system.

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