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What the Tongue Tells the Brain about Taste

Marion E. Frank and Thomas P. Hettinger

University of Connecticut Health Center, Farmington, CT, USA

Correspondence to be sent to: Marion E. Frank, e-mail: mfrank@neuron.uchc.edu

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The essence of coding taste quality

The chemical stimuli of special significance to taste are sugars (sweet), amino acids (umami), sodium chloride and other salts (salty), alkaloids (bitter) and acids (sour). Sugars and amino acids tend to be preferred, while alkaloids and acids tend to be avoided. Intake of salts depends on electrolyte balance. The gustatory system codes taste qualities and their associated hedonic attributes. The ability to distinguish foods from poisons is so important that it is hard-wired in the receptor cells themselves. Yet despite teleological appeal, neither nutritional value nor toxicity is a stimulus dimension that is coded *per se*. Sweet and bitter may be considered metaphors for nutritious and toxic, respectively. Toxicity and nutrition are not chemical properties of a stimulus nor are they properties of the senses. They are defined in terms of critical metabolic events, most of which are beyond sensation. For example, sucrose and saccharin are both sweet, but saccharin has no caloric value. Salts such as NaCl and LiCl have similar tastes, yet lithium salts are toxic but sodium salts are not. There are many examples of neurotoxins that are tasteless yet extremely toxic. Strychnine and sucrose octaacetate (SOA) are both bitter, though strychnine is toxic while SOA is not.

The taste receptor cells define taste quality

Some of the molecular receptors responsible for taste stimulus detection have recently been identified. It has been known for ~20 years that sodium detection, at least in some mammals, involves amiloride-sensitive epithelial sodium channels. This was the first taste receptor system that could be defined on a molecular basis (see review by Hettinger and Frank, 1992).

The T1R and T2R taste receptors responding to sugars, amino acids and bitter stimuli have a distribution that is restricted to taste bud cells (for a review, see Montmayeur and Matsunami, 2002). Furthermore, they tend to occur in combinations, with T1R1/T1R3 (umami) receptors often found in one group of cells and T1R2/T1R3 (sweet) receptors in a different population of cells. Many of the large family of T2R (bitter) receptors appear combined in another population of taste cells. This has been interpreted as indicating that these three classes of taste cells are the substrate for defining umami, sweet and bitter sensations. Support for this idea has been obtained by studying knockout mice that lack one or more of these receptors. In a critical test of taste coding by taste receptor cells (Zhao *et al.*, 2003), mice were genetically engineered to express in their taste cells a receptor for a synthetic opioid that is normally tasteless. When the receptor was expressed only in cells that normally respond to sweet stimuli, the mice found the taste of the opioid attractive. These results fit a Müllerian model of sensory coding: the taste cells presumably code sweetness no matter how the cells are stimulated.

The roles of peripheral nerves

A number of studies have suggested that peripheral neurons receive input from several taste cells and taste buds. This raises the issue of whether individual neurons have diverse inputs and have stimulus selectivity different from the taste receptor cells. Numerous investigations of single nerve fibers have indicated both specific and broad tuning, though it has not been established how the tuning of the fibers relates to the tuning of taste cells. There is a clear association between the patterns of activation of sucrose- and sodium-selective chorda tympani fibers and quality-specific behavioral responses (Frank, 2000). The different sensory fields of the tongue, in particular the chorda tympani and glossopharyngeal fields, supply different information to the brain. The posterior portion of the tongue is involved more in reflex actions than the anterior tongue.

Taste modulators

It is evident that the tongue already segregates the substrates for taste quality for transmission to the brain. The tongue can also modulate taste intensity as seen in the inhibition of saltiness by chlorhexidine, sweetness by gymnemic acid and bitterness by sodium chloride in humans. However, these modulators appear only to affect taste intensity, not taste quality.

Taste mixtures

In humans and animals component qualities remain separate in mixtures. Intensities may be suppressed without synthesis of new qualities.

Anesthetics

General anesthetics have a depressive action on excitatory neurons in the central nervous system. Taste signals from the tongue are able to reach the brain, but the ability of the brain to interpret these signals is compromised. Cortical regions, far removed from sensory input, would show the greatest distortion.

Differing functions of the taste system

Besides coding for taste quality, the taste system has to establish the hedonic value of the stimulus. The latter is one of the complex functions of the brain that requires integration with the nutritional needs of the organism. Also, reflex actions of the taste system, such as salivation, may use some of the same sets of receptors used for quality detection, though pathways quickly become separate in the brain stem.

Conditioned taste aversions result in modified activity in several parts of the brain, including the brain stem. However, the information transmitted by the tongue is probably no different than in the unconditioned state. In fact, the use of conditioned taste aversions has been a key approach to determining how animals classify taste stimuli (Frank and Nowlis, 1989).

Species differences

Most sensory systems demonstrate a clear evolutionary homology. However, it must be recognized that, for the gustatory system to function within the confines of the differing needs of various species, there will necessarily be important phylogenetic differences in taste function. Visual systems differ greatly between species in how and whether color is discriminated. Humans and great apes are trichro-

mats, while most other mammals are dichromats. Some rodent species such as hamsters may have only a single type of cone and thus may be completely colorblind. No less of a distinction should be expected for taste. A number of behavioral and electrophysiological studies have shown large species differences in taste. It has been argued that the taste systems of various species are intimately connected with their nutritional needs (Boudreau *et al.*, 1985). For example, the significance of sweetness, saltiness and bitterness in carnivores would be expected to be different from that of herbivores and omnivores. There are large differences in taste sensitivity of various species to most taste stimuli. As with color vision, there is no assurance that different species even perceive the same taste qualities.

Not all stimuli that are perceived as sweet in humans are recognized as such by other animals. Aspartame and miraculin are sweet in humans and great apes but not in most other animals. Species diversity is particularly apparent with bitter stimuli. Rodents can detect ~0.3 μM cycloheximide, yet humans require ~1 mM, a difference factor of ~3000. On the other hand, humans can detect ~0.01 μM denatonium benzoate, while rodents require ~0.3 mM for detection, a difference factor of ~30 000. The overall factor describing the human-rodent disparity between cycloheximide and denatonium sensitivity is ~90 000 000 (unpublished data).

The cycloheximide receptor has been identified as mT2R5 in mice and its rat ortholog as rT2R9 (Chandrashekar *et al.*, 2000). The rodent receptors respond to cycloheximide in the behaviorally relevant micromolar range. The closest human ortholog hT2R10 does not respond to cycloheximide, consistent with the behavioral data. The extreme sensitivity of humans to denatonium has not been explained by responses of any of the known T2 receptors. The threshold of the human receptor hT2R4 for denatonium *in vitro* is ~100 μM (Chandrashekar *et al.*, 2000), a concentration that is still ~10 000 times higher than the human taste detection threshold. Denatonium is structurally similar to QX-314 and lidocaine, known blockers of cation channels (Hille, 1992). The substitution of an ethyl group in QX-314 by a benzyl group in denatonium would likely increase receptor affinity and give a lower threshold. Denatonium as well as other organic cations may function as bitter stimuli in humans by blocking cation channels rather than by interaction with G-protein coupled T2 receptors.

Comparison of taste and vision

The distinction between how the taste system works compared to vision is now fairly clear and is dependent on fundamental differences in their molecular receptors. In color vision, receptors are by their very nature broadly tuned due to the broad absorption spectra of the retinal chromophores that respond to a continuous wavelength dimension. This significant feature is used by the visual system to detect and distinguish an enormous variety of colors by comparing the relative activity of just three cones. The taste system, on the other hand, has developed a set of molecular receptors that can be highly selective for particular taste stimuli. There is no continuous stimulus dimension in taste, but instead there are discrete classes of stimuli such as carbohydrates, amino acids, alkaloids, acids and salts that are recognized by discrete classes of receptors. This is what the tongue tells the brain about taste.

Summary

The tongue translates a chemical taste signal into a neural code that the brain can interpret. How it does that is still a mystery, but the key elements are known. Specific molecular taste receptors on taste receptor cells located in the taste buds bind taste stimuli. Through complex transduction schemes and synaptic activation of neurons, stimulus information is sent to the brain by peripheral neurons. There is a close correspondence between the stimulation of particular types of taste receptor cells, the activation of classes of peripheral taste nerve fibers and the evoked taste qualities. In humans, these perceptions are defined as sweet, umami, salty, sour and bitter. Incomplete homologies may exist for other species. The tongue tells the brain about taste quality, but the brain bypasses the quality assignment in brainstem reflexes and assesses the qualities for hedonic value.

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