Nutrient Tasting and Signaling Mechanisms in the Gut

IV. There is more to taste than meets the tongue

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Katz, Donald B., Miguel A. L. Nicolelis, and S. A. Simon. Nutrient Tasting and Signaling Mechanisms in the Gut. IV. There is more to taste than meets the tongue. Am. J. Physiol. Gastrointest. Liver Physiol. 278: G6–G9, 2000.—The tongue is the principal organ that provides sensory information about the quality and quantity of chemicals in food. Other information about the temperature and texture of food is also transduced on the tongue, via extrajugal receptors that form branches of the trigeminal, glossopharyngeal, and vagal nerves. These systems, together with information from the gastrointestinal (GI) system, interact to determine whether or not food is palatable. In this themes article, emphasis is placed on the integrative aspects of gustatory processing by showing the convergence of gustatory information with somatosensory, nociceptive, and visceral information (from the GI system) on the tongue and in the brain. Our thesis is that gustation should be thought of as an integral part of a distributed, interacting multimodal system in which information from other systems, including the GI system, can modulate the taste of food.

**MULTIMODAL SYSTEM; VISERAL SYSTEM; CENTRAL NERVOUS SYSTEM; TRANSDUCTION**

THE TONGUE PROVIDES an organism's first internal analysis of potentially ingestible stimuli. The sensory mechanisms embedded in lingual epithelium are used to distinguish chemical compounds that are potentially nutritive (e.g., salts, sugars, proteins, carbohydrates, fats, and so forth) from those that are potentially harmful (e.g., bitter-tasting plant alkaloids). In addition, these sensors extract information about the texture and temperature of food. Such judgments prepare the gastrointestinal (GI) system for compounds in the mouth by causing the organism to salivate, masticate, swallow, or expel, as well as to release insulin and other peptides.

Of course, the tongue is also the gateway into the gustatory perceptual system, wherein the “tastes” of stimuli (qualitative judgments about similarities between tastants) are processed. Typically, this process has been discussed with regard to specific transducers on the tongue, called taste buds, that contain taste receptor cells (TRCs; Fig. 1). In this brief themes article, we outline recent work describing the complexities of taste transduction and discuss a more global aspect of taste that includes somatosensory, nociceptive, and visceral pathways. It is our contention that the study of “taste” is inextricably linked to the study of GI and somatosensory/nociceptive function. The gustatory system is part of a large, interacting multimodal system processing not simply tastants or nutrients but the acceptability and palatability of food.

**STIMULUS TRANSDUCTION ON THE LINGUAL EPITHELIUM**

The dorsal surface of the tongue is a stratified squamous epithelium containing nerve endings that transduce a variety of stimulus attributes. Receptors distributed throughout the tongue, palate, and esophagus transmit information to the brain regarding a stimulus' temperature, shape, texture, elasticity, size, chemical quality, and intensity.

Taste transduction involves specialized “onion-shaped” structures, called taste buds, that are distributed throughout the oral cavity. Taste buds comprise 50–100 individual TRCs whose apical and basal sides are separated by cation-selective tight junctions, so called because they are permeable only to small cations and anions. Because of their moderate cation selectivity, tight junctions can influence the taste of salts and acids. The restricted diffusion of anions provides a rational explanation of why NaCl tastes different from sodium gluconate and why citric acid tastes different from HCl (8, 17).

The recent application of sensitive optical and electrophysiological methods, in conjunction with techniques from molecular biology, has led to marked advances in the understanding of taste transduction mechanisms (10). Taste cells contain a plethora of ligand-gated ion channels, transporters, pumps, and synaptic machinery that are not commonly found in other epithelial cells. These include voltage-dependent Na+ and K+ channels, ligand-gated ion channels, and synaptic machinery that are not commonly found in other epithelial cells. These include voltage-dependent Na+ and K+ channels, ligand-gated ion channels, and synaptic machinery that are not commonly found in other epithelial cells.
nels (ASSC) that are also found in other transporting epithelia, such as the large intestine (9a).

Space considerations do not permit a very detailed discussion of all specific transduction mechanisms, so we will review them only briefly. We refer interested readers to excellent reviews by Lindemann (12) and Herness and Gilbertson (9a). TRC activation occurs via two general mechanisms, both of which result in the release of transmitters (e.g., serotonin) onto primary gustatory neurons. One involves the direct gating of ion channels by compounds (some amino acids, Na\(^{+}\)) that depolarize TRCs and activate voltage-dependent Ca\(^{2+}\) channels, thereby permitting the entry of Ca\(^{2+}\) into the cell. The second method involves activation of G protein-coupled receptors (GPCRs) by complex sweet- and bitter-tasting compounds, as well as by some amino acids. The identification of GPCRs for tastants has been slow, but recent success in cloning a putative taste receptor suggests that rapid progress will now be made (10). Activation of TRCs stimulates a variety of second messenger systems that either lead to the release of Ca\(^{2+}\) from intracellular stores or modulate ion channels that depolarize the cells, again permitting the entry of Ca\(^{2+}\) into the cell. In each case, Ca\(^{2+}\) influx leads to transmitter release.

The primary gustatory neurons are branches of cranial nerves VII, IX, and X (Fig. 1). The chorda tympani nerve (VII) innervates the anterior tongue, the superficial petrosal nerve (VII) the palate, the glossopharyngeal nerve (XI) the posterior tongue, and the vagal nerve (X) the esophagus and epiglottis. All of these nerves project to the nucleus of the solitary tract (NTS) in the medulla (Fig. 1).

Much is known about the transduction mechanisms of salt (NaCl) taste. Na\(^{+}\) depolarizes TRCs by diffusing across ASSCs [which, in TRCs, are very similar to the recently cloned epithelial Na\(^{+}\) channels (ENaC)], whereas Cl\(^{-}\) diffuses across the tight junctions. ASSCs on the tongue are regulated by hormones that are involved in water and electrolyte balance (antidiuretic hormone, aldosterone), which in rats mediate a Na\(^{+}\)-specific appetite.

Because protons activate virtually all TRCs, and because they can affect so many transport processes, it has been difficult to isolate the origin of sour taste. It has been shown that TRCs can become depolarized by
the diffusion of protons through ASSCs, but this mechanism alone is not sufficient to explain sour taste transduction. Other experiments have shown that lowering the extracellular pH decreases intracellular pH, which could result in an increase in intracellular Ca\(^{2+}\) (13, 17). In addition, RT-PCR and in situ hybridization studies reveal the presence of subunits of proton-gated ion channels that are members of the MDEG/ENaC superfamily that may also be involved in sour taste (13). In summary, it appears that sour taste involves several transduction mechanisms.

Transduction of sweet-tasting compounds involves activation of GPCRs on the apical surface of TRCs. The particulars of the cascade depend on a number of factors, including the specifics of the taste stimulus. In the case of saccharides, activation of the GPCR will activate adenylate cyclase, increasing cAMP that will either directly or indirectly (via cAMP-dependent protein kinase) close basolateral K\(^+\) channels, depolarizing TRCs. Synthetic sweeteners such as saccharine and \(\alpha\)-amino acids activate a different GPCR that in turn activates phospholipase C (PLC) to produce inositol trisphosphate (IP\(_3\)) and diacylglycerol. The former increases intracellular Ca\(^{2+}\), and the latter phosphorylates and closes basolateral K\(^+\) channels. Both pathways can coexist in the same TRC (2). Recent evidence obtained in transgenic mice suggests that gustducin, a taste-specific G protein that has marked homology to transducin (and that is also present in TRCs), may be involved in the transduction of both saccharides and natural sweeteners (19).

As with sweeteners, there are many chemically distinct classes of bitter-tasting compounds. Many of these are alkaloids, like quinine and nicotine; others are \(\alpha\)-amino acids, urea, and even salts (e.g., MgCl\(_2\)). Not all of these bitter tastants use the same transduction pathways. Most of the organic compounds appear to be coupled to GPCRs, but quinine can directly inhibit a variety of ion channels. One mechanism that encompasses the transduction of numerous bitter tastants involves the activation of PLC and production of IP\(_3\). Gustducin knockout mice exhibit impaired responses to bitter compounds, suggesting that gustducin (transducin) is involved in both sweet and bitter transduction (19).

Most of the work concerning amino acid transduction in mammalian TRCs has centered on investigating the effects of \(\alpha\)-glutamate, which involves both ionotropic and metabotropic (mGluR4) glutamate receptors (6). It is likely that receptors for other amino acids will soon be discovered.

One central issue in gustatory physiology regards the relationship between taste transduction and gustatory coding throughout the gustatory axis. Because food consists of many different chemical categories, it is clearly important to understand the chemical selectivity of individual TRCs (in different regions of the oral cavity) at the most peripheral level. Present information reveals that most TRCs can be activated by more than one chemical stimulus. In other words, there is not, for example, a TRC that will respond exclusively to a single chemical. Nevertheless, TRCs exhibit some chemical selectivity, and most will respond “best” to one of the many stimuli tested. Thus the encoding of a unique taste begins by the activation of broadly tuned TRCs. How this information is then transmitted and modulated throughout the gustatory axis represents a major challenge in gustatory physiology.

**INTERACTIONS BETWEEN TRANSDUCTION MECHANISMS ON THE LINGUAL EPITHELIUM**

The epidermis and papillary layers of the anterior tongue also contain thermosensitive, mechanosensitive, and nociceptive trigeminal neurons (Fig. 1). Although relatively little is known about the peripheral interactions between these systems, there is evidence to suggest that activation of intraganglial and periganglial nociceptors or of nociceptors on blood vessels by capsaicin (the pungent compound in hot pepper), acid, or high temperatures (Fig. 1) can modulate gustatory responses. Activation of these nociceptors will induce them to release peptides (e.g., substance P, calcitonin gene-related peptide) that can bind to receptors on TRCs and blood vessels and modulate their activity by either activating second message cascades in TRCs and/or by vasodilatation, which will change the tongue’s temperature and hence gustatory responses. Very little is known about the interaction between these two systems anywhere in the gustatory axis, and it is our view that such information is important in the understanding of gustatory coding (see below).

**CENTRAL NERVOUS SYSTEM PHYSIOLOGY AND CONVERGENCE OF MODALITIES**

Integration of sensory information is more apparent in the central nervous system gustatory axis, where gustatory, somatosensory, nociceptive, and visceral responses converge on many of the same nuclei. Figure 1 presents the primary taste pathways in the mammalian brain. Primary gustatory neurons from cranial nerves VII, IX, and X converge massively onto neurons in the anterior NTS. Vagal afferents from the viscera converge on the posterior NTS and may interact with gustatory neurons via NTS interneurons. Anatomic research reveals that collaterals from the lingual branch of the trigeminal nerve also cause tongue-related cutaneous information to converge with gustatory information in the NTS (18).

From the NTS, taste- and viscera-related activity is relayed to the parabrachial nuclei (PBN) in the pons and amygdala and from the PBN to the thalamus and amygdala. Both thalamus and amygdala project to primary gustatory cortex. Mingling of gustatory with nociceptive, cutaneous, and visceral information occurs in some form at all of these sites (1, 7, 14–16, 20, 21). The processing of taste information, relayed from TRCs, thus seems closely integrated with information regarding texture and temperature and with responses from the GI system. The gustatory perceptual system seems to be more rightly regarded as part of a larger system designed to deal with the wholistic consumptive experience.
BEHAVIORAL CORRELATES

The systemic nature of gustation is obvious to any well-fed person who has ever put a soft potato chip, a soggy slice of bread, or a rubbery celery stalk into his or her mouth. Clearly, palatability involves integration of gustation with somatosensation.

Taste psychophysicists have noted, furthermore, that somatosensory or nociceptive input in the oral cavity may be “misinterpreted” as a gustatory sensation. For instance, the so-called “astringent taste” is actually a “mouth feel” phenomenon caused by the precipitation of proline-rich proteins in saliva (4). The presence of capsaicin, the principal ingredient in hot pepper, changes the perception of a variety of tastes, despite acting mainly on nociceptors (11).

The well-studied phenomenon of conditioned taste aversion demonstrates the interaction between taste-related and visceral sources of information. When strong emetic stimuli (e.g., LiCl) activate the visceral system in the hours following the intake of a food, animals will thereafter avoid that food (3). Neural responses to the newly aversive food also change, becoming more like responses to bitter stimuli (5, 9, 22). The robustness of this learning (9, 21) suggests that it reflects a basic purpose of the taste system: a general process in which taste quality is modulated as a function of the GI consequences of ingestion.

In conclusion, we have presented an integrative framework in which to explore gustatory function. Future studies will need to consider taste not as a separate entity but as a phenomenon related to the processing of multiple modalities.

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