Taste Receptors in the Gastrointestinal Tract

III. Salty and sour taste: sensing of sodium and protons by the tongue

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DeSimone, John A., and Vijay Lyall. Salty and sour taste: sensing of sodium and protons by the tongue. Am J Physiol Gastrointest Liver Physiol 291: G1005–G1010, 2006. First published June 29, 2006; doi:10.1152/ajpgi.00235.2006.—Taste plays an essential role in food selection and consequently overall nutrition. Because salt taste is appetitive, humans ingest more salt than they need. Acids are the source of intrinsically aversive sour taste, but in mixtures with sweeteners they are consumed in large quantities. Recent results have provided fresh insights into transduction and sensory adaptation for the salty and sour taste modalities. The sodium-specific salt taste receptor is the epithelial sodium channel whereas a nonspecific salt taste receptor is a taste variant of the vanilloid receptor-1 nonspecific cation channel, TRPV1. The proximate stimulus for sour taste is a decrease in the intracellular pH of a subset of acid-sensing taste cells, which serves as the input to separate transduction pathways for the phasic and tonic parts of the sour neural response. Adaptation to sour arises from the activation of the basolateral sodium-hydrogen exchanger isoform-1 by an increase in intracellular calcium that sustains the tonic phase of the sour taste response.

SALTY AND SOUR REPRESENT TWO of the five primary taste qualities, the others being sweet, bitter, and umami (the “meaty” taste of glutamate and certain other L-amino acids). These qualities exert a powerful influence on food selection and consequently overall nutrition. Humans and many other mammals innately regard sweet and umami stimuli as appetitive whereas moderately to strongly sour and bitter tasting foods are aversive and usually rejected on the basis of a simple taste assay (2). However, as most of us are aware, when ingestion of a taste-aversive substance can produce desirable postigestive effects, as in the case of alcohol and caffeine, individuals condition themselves to accept those tastes as hedonically positive. Taste sensitivity to salty stimuli appears to develop postnatally in both humans and laboratory rats (2, 8). The hedonic value of NaCl, physiologically the most important dietary salt, varies to some extent with the subject’s sodium needs. Sodium-depleted subjects display a lower salt taste threshold than sodium-replete subjects and increased preference for high-salt diets normally found to be aversive in sodium-replete subjects (1). The fact that salt taste sensation is affected by systemic conditions that result in increased levels of aldosterone suggests that salt taste reception may involve one of that hormone’s cell sodium transporter targets. This is in fact the case and, as discussed below, evidence indicates that the epithelial-sodium channel (ENaC) is the mammalian Na⁺-specific taste receptor. In addition, most mammals have at least one more salt taste receptor that is cation nonselective, the existence of which is apparent from the salty taste evoked by KCl and NH₄Cl. Because salt taste is generally appetitive, even for sodium-replete individuals, people in developed countries ingest far more salt than is required to maintain a normal sodium balance (25). Although this is of little consequence to normotensive subjects, a large subgroup with essential hypertension, the so-called salt-sensitive group, responds to increased salt intake with a corresponding increase in blood pressure (25). Both normotensive and salt-sensitive individuals are advised in the Dietary Guidelines for Americans 2005 of the Department of Health and Human Services to limit sodium intake to 2,300 and 1,500 mg/day, respectively. Not surprisingly, these recommended levels are difficult to maintain considering that regular servings of processed foods that most of us enjoy approach these daily levels. For example, a 4 oz. piece of cheese pizza can contain as much as 1,200 mg of sodium. Accordingly, one of the possible benefits of a thorough understanding of salt taste receptor mechanisms, described below, may be the discovery of novel ways of maintaining the sensation of salty even at reduced dietary sodium levels.

Sourness is uniquely evoked by acids, and it is evident that limiting the ingestion of acids from foods and beverages is part of the body’s overall strategy in maintaining acid-base homeostasis. Sour taste aversion is sufficiently potent so that the ingestion of acids is only tolerable when sourness is masked with sweet- or salty-tasting substances, for example by the addition of artificial and natural sweeteners to soft drinks and other acidic beverages. So although drinking citric acid or phosphoric acid alone may be intolerable, citric acid and sucrose are consumed as lemonade and other fruit juice drinks; similarly, phosphoric acid, carbonic acid, and sucrose or artificial sweeteners form the basis of many popular carbonated soft drinks. By masking sour taste we manage to ingest large quantities of acids daily, probably more than Nature intended given the aversiveness of sour taste per se. Although under normal circumstances the lungs and kidneys seem to deal adequately with increased acid load, the combination of increased acid and sugar in foods and beverages leads unavoidably to low pH in the oral cavity, which promotes tooth enamel demineralization directly and indirectly by encouraging the growth of acid-tolerant bacteria that are themselves strong acid secretes. The high titratable acidity of citrus drinks and juices and the low pH of soft drinks are also associated with more reported cases of heartburn. With new insights into sour taste transduction mechanisms, as described below, it may be possible to develop means of maintaining a desired level of sourness even at reduced levels of dietary acids.
ENaC, the Na⁺-Specific Salt Taste Receptor

The Na⁺-specific salt taste receptor is especially evident in herbivores, where it plays an essential role in their foraging for Na⁺. For example, when sodium-deficient wild rabbits are given the opportunity to choose a salt lick from among various mineral salts made available to them, they assay them (i.e., taste them) at random, then reject all but the Na⁺ salts (3). Their high circulating aldosterone levels suggest aldosterone-modulated epithelial cell membrane Na⁺ transporters as candidate salt taste receptors. Consistent with this, numerous studies indicate that ENaC is the Na⁺-specific salt taste receptor. Consistent with this, numerous studies indicate that ENaC is the Na⁺-specific salt taste receptor in mammals. The α-, β-, and γ-ENaC subunits are present in rat fungiform papilla taste cells (10, 20), and injection of rats with aldosterone increased apical taste cell membrane immunoreactivity to β- and γ-ENaC, increased the number of fungiform taste cells with amiloride-sensitive currents, and enhanced the magnitude of the Na⁺ current (11).

Consistent with the wide distribution of ENaC in both sensory and nonsensory epithelia, the dorsal lingual epithelium is a Na⁺-transporting epithelium in various mammalian species (23). That taste receptor cells are also Na⁺ transporting can be verified directly in whole cell patch clamp studies and by direct measurement of unilateral apical Na⁺ flux in polarized taste receptor cells (13, 23). Studies on isolated rat and hamster taste buds show that amiloride blocks a Na⁺ current across taste cell membranes, supporting a role for ENaC in Na⁺ transport in various species (23). That taste receptor cells are also Na⁺ transporting can be verified directly in whole cell patch clamp studies and by direct measurement of unilateral apical Na⁺ flux in polarized taste receptor cells (13, 23). Studies on isolated rat and hamster taste buds show that amiloride blocks a Na⁺ current across taste cell membranes, supporting a role for ENaC in Na⁺ taste reception (23). The most direct evidence in support of ENaC as a Na⁺-specific taste receptor protein is that, in various species, taste nerve responses to NaCl are significantly inhibited by amiloride or its more potent analog, benzamil. Taste responses to NaCl recorded in the afferent chorda tympani or in the nucleus of the solitary tract of various species are significantly inhibited by amiloride without effect on responses to stimuli of other taste modalities (23). Amiloride sensitivity is observed in single chorda tympani units of the chimpanzee that respond strongly to Na⁺ and Li⁺ salts, but not in units sensitive to both Na⁺ and K⁺ (7). More generally salt-sensitive chorda tympani responses fall into two categories: Na⁺- (and Li⁺-) specific units that are inhibited by amiloride or benzamil, and cation-nonsensitive units that are amiloride or benzamil insensitive. These data support the concept of two (or more) salt taste receptor types, one that responds specifically to Na⁺ salts (i.e., ENaC) and one (or more) that responds to various cations (see Fig. 1). In rodents the amiloride-sensitive part of the chorda tympani response to NaCl is typically 70% or more of the total. This has profound behavioral consequences as studies on rats demonstrate. A rat’s ability to discriminate between NaCl and KCl depends on information from the chorda tympani, and this ability is progressively lost with NaCl solutions containing increasing amiloride concentrations, i.e., when the animal is denied the benefit of neutral input from taste cell ENaC (22). The gradual loss of Na⁺ discrimination by behaving rats given NaCl solutions with increasing amiloride concentrations is in good agreement with the amiloride concentration dependence of the diminution of the response to NaCl in Na⁺-sensitive single units of the nucleus of the solitary tract. On balance, the molecular, immunocytochemical, electrophysiological, and behavioral data support the conclusion that ENaC is uniquely the Na⁺-specific salt taste receptor.

It is interesting to note, however, that taste cells from rat circumvallate papillae in the posterior tongue that are innervated by the glossopharyngeal nerve give only amiloride-insensitive neural responses to NaCl (23). This is surprising because ENaC can be detected in circumvallate taste cells (10). The reason for the lack of function may be that only the

![Fig. 1. Model for Na⁺ transport in fungiform papilla taste receptor cells and salt taste transduction in the anterior tongue. ENaC, amiloride-sensitive epithelial Na⁺ channel (green); TRPV1t, taste variant of vanilloid receptor-1 (red); NHE-1, basolateral Na⁺-H⁺ exchanger-1; NHE-3, apical Na⁺-H⁺ exchanger-3; Bz, benzamil; ETH, ethanol; CZP, capsazepine; RTX, resiniferatoxin; SB-366791, N-(3-methoxyphenyl)-4-chloro-rocininamide; [Na⁺], external Na⁺; CT, chorda tympani; paracellular shunt (dark blue); VGCC, voltage-gated Ca²⁺ channels; ↔, no change; ↑, increase; ↓, decrease. Although shown here as present in the same cell, ENaC and TRPV1t may actually be expressed separately in different taste receptor cell types. (Adapted from The Journal of General Physiology, 2005, vol. 125, p. 587–600 by copyright permission from The Rockefeller University Press.)](http://ajpgi.physiology.org/
α-subunit of ENaC is found there in abundance. After aldosterone injection, however, an amiloride-sensitive Na⁺ current can be detected in circumvallate taste cells, where amiloride-sensitive currents are otherwise absent (11). This suggests the presence of a latent population of specific Na⁺-detectors in the posterior lingual taste field that can be activated under environmental conditions resulting in high aldosterone levels. Although such conditions may arise routinely in the case of foraging herbivores, they are unlikely to be encountered by humans today given the wide availability of dietary salt. It is perhaps for that reason that amiloride suppresses NaCl taste intensity in Na⁺-replete human subjects (healthy young Americans) by only 21%, i.e., in these humans the amiloride-insensitive component of the taste response to NaCl accounts for nearly 80% of the response (21). This is just the opposite of what is found in rodents. Diet may play an important role in determining the extent to which the ENaC salt taste receptor is insensitive component of the taste response to NaCl accounts for nearly 80% of the response (21). This is just the opposite of what is found in rodents. Diet may play an important role in determining the extent to which the ENaC salt taste receptor is expressed because Na⁺-specific, amiloride-sensitive taste units are found in abundance in the chorda tympani nerves of mainly vegetarian primates including the chimpanzee (7). There appears to be some heterogeneity in the human population with respect to the amiloride sensitivity of NaCl taste. Changes in lingual surface potential (LSP) with increasing NaCl concentration were measured in human subjects (5). On average, amiloride reduced the LSP response to NaCl by ~19%, in good agreement with the mean decrement in perceived salt taste intensity (21). However, in some subjects amiloride reduced the LSP by as much as 42%, whereas in others it reduced the LSP by <5% (5).

TRPV1t, a Nonspecific Cation Taste Receptor

Single unit analysis of salt taste responses indicates the presence of at least one more salt taste receptor that responds to a variety of cations including Na⁺, K⁺, NH₄⁺, and Ca²⁺ and is amiloride insensitive (7, 23). These units are distinct from the amiloride-sensitive Na⁺-specific fibers, suggesting that amiloride-sensitive and amiloride-insensitive salt taste responses may originate from different receptor cell types. Evidence to date indicates that one nonselective cation taste receptor is a variant of TRPV1, the nonselective cation channel in nociceptive neurons that mediates thermal pain including the noxious thermal pain produced by vanilloids such as capsaicin and resiniferatoxin. The amiloride-insensitive component of the NaCl chorda tympani response, as well as the responses to KCl, NH₄Cl, and CaCl₂ in rat, are enhanced by resiniferatoxin and capsaicin with increasing concentration up to a maximum enhancement and at higher vanilloid concentrations the neural responses are suppressed, i.e., the vanilloid concentration vs. salt-evoked chorda tympani response relations are bell shaped (17). Additional observations, summarized in Fig. 1, support the hypothesis that at least one of the amiloride-insensitive salt taste receptors in fungiform papilla taste buds is a taste variant of TRPV1 (TRPV1t) (17). The tonic part of the amiloride-insensitive NaCl chorda tympani response is completely inhibited by SB366971, a TRPV1 inhibitor. The effects of temperature and vanilloids on the amiloride-insensitive NaCl chorda tympani response are additive, similar to TRPV1. Increases in temperature and in vanilloid concentration, in turn, increase the response conductance (slope of the normalized chorda tympani response with voltage applied to the anterior lingual receptive field), i.e., the taste receptor has ion channel characteristics in situ. Vanilloids, external pH, and ATP shift the increase in the neural response to NaCl with temperature to a lower temperature threshold in a manner analogous to their effects on TRPV1. A TRPV1 mRNA transcript common to several channels in the transient receptor potential (TRP) receptor family was detected in rat fungiform taste cells (12). TRPV1 knockout mice lack a tonic phase amiloride- or benzamil-insensitive NaCl chorda tympani response whereas control mice display the full phasic and tonic NaCl response. Ethanol is an agonist of the amiloride-insensitive salt taste response (16) similar to its agonistic effect on TRPV1. The structure of TRPV1t is still undetermined, but there are reasons to suggest that it may differ somewhat from TRPV1. First, TRPV1t is constitutively active, whereas TRPV1 channel is nonconducting unless activated by heat, acidic pH, or the presence of vanilloids. Second, a decrease in pH alone (i.e., in the absence of an agonist) has no effect on TRPV1t whereas lowering pH activates TRPV1. The taste variant TRPV1t cannot detect an increase in food acidity and can, therefore, function as a salt taste receptor, but not, therefore, as a sour taste receptor (12). It is important to note, however, that TRPV1 knockout mice still display a truncated phasic response to NaCl. This suggests that in addition to TRPV1t yet another amiloride-insensitive salt taste sensor may exist.

Sour Taste Transduction

Because all sour stimuli are acids, it would appear reasonable to assume that sour taste intensity should be proportional to stimulus pH. However, human taste studies indicate otherwise. For example, acetic acid is more intensely sour than HCl at the same pH (4). Because salivary flow rate is proportional to sour taste intensity, it is possible to show that sour taste is more closely associated with the amount of titratable acid in the stimulus rather than its pH (4). Recordings from the rat chorda tympani support this conclusion (4). The fact that titratable acid correlates better with sourness than stimulus pH suggests that the initial event in sour transduction is the transfer of protons or acid equivalents from the stimulus to sites on or within sour taste receptor cells. The preponderance of evidence indicates that these sites are intracellular, because upon stimulation with acid the decrease in intracellular pH (pHᵢ) of a subset of taste receptor cells correlates well with the intensity of neural signal obtained for various acids (13–15, 18). Thus the proximate sour stimulus is a decrease in pHᵢ in acid-sensing taste receptor cells.

Weak organic acids, such as acetic acid and citric acid (i.e., those found naturally in foods) and CO₂ (carbonic acid precursor), enter taste cells by diffusion across the lipid bilayer as neutral molecules. That the sour stimulus is a decrease in pHᵢ is readily demonstrated in the case of carbonic acid, which is formed intracellularly by the carbonic anhydrase catalyzed hydration of CO₂. Inhibiting carbonic anhydrase activity with the membrane-permeable inhibitor MK-417 significantly reduced the decrease in taste receptor cell pHᵢ to a stimulus of 10% CO₂ buffered at a fixed extracellular pH of 7.4 and inhibited both the phasic and tonic chorda tympani response to CO₂ (14). Further evidence indicating pHᵢ as the proximate sour stimulus is that the same concentration of buffered acetic acid (pH 6) and unbuffered acetic acid (pH ~3) produces an...
equivalent decrease in taste cell pH and an equivalent chorda tympani response (14). Strong mineral acids such as HCl are fully dissociated at any pH, so that taste cell acidification by strong acids must involve proton transporters, i.e., proton channels or ion exchangers. Evidence indicates the presence of strong acids must involve proton transporters, i.e., proton channels or ion exchangers.

Fig. 2. Model for acid transport in fungiform papilla taste receptor cells and sour taste transduction in the anterior tongue. A: proposed acid transporters in taste receptor cell membranes. B: acid-induced decrease in taste receptor cell pH causes cell shrinkage and the activation of a flufenamic acid-sensitive shrinkage-activated nonselective cation channel that is involved in eliciting the phasic part of the chorda tympani response to acidic stimulation (P). C: in a subset of taste receptor cells a decrease in pH induces an increase in intracellular Ca²⁺ concentration ([Ca²⁺]), which in turn activates the basolateral NHE-1. Activation of NHE-1 is responsible for pH, and cell volume recovery and for the observed level of neural adaptation (tonic response; T) in the chorda tympani response to acidic stimuli. ER, endoplasmic reticulum; H⁺-gated channels (HCN, hyperpolarization-activated channel; ASIC, acid-sensing ion channel; TASK-2, a two-pore domain K⁺ channel); NHE-1, basolateral Na⁺-H⁺ exchanger; NHE-3, apical Na⁺-H⁺ exchanger; SANSCC, shrinkage-activated nonselective cation channel; VGCC, voltage-gated Ca²⁺ channels; ↓, increase; ↓, decrease. (Adapted from The Journal of General Physiology, 2006, vol. 127, p. 15–34 by copyright permission from The Rockefeller University Press.)

**Sour Phasic Response**

Typically, the neural response to all taste modalities consists of a rapid phasic burst of action potentials peaking in frequency in 1–2 s followed by a rapid decline to a pseudo-steady state (tonic response level). The tonic level includes the effect of sensory adaptation on the response. Figure 2 illustrates schematically the intracellular signaling effectors involved in the phasic and tonic components of a sour taste neural response. From imaging studies on fungiform papilla taste buds, maintained in their normal polarized orientation in the lingual epithelium, intracellular acidification causes rapid taste cell shrinkage (18). This is not osmotic shrinkage because it occurs in both hypoosmotic and isoosmotic media. However, osmotically preshrinking the taste cells in hyperosmotic mannitol will reduce the extent to which acidification can further reduce cell volume (18). As illustrated in Fig. 2B, taste cell shrinkage, induced by a decrease in pH, involves a change in the taste cell cytoskeleton F-actin to G-actin equilibrium; F-actin is converted to G-actin by a decrease in pH (18). This conversion may be part of a more general mechanism of pH-induced, isosmotic cell shrinkage that basically operates through neutralization of fixed cytoskeletal protein negative charges. As a consequence, the repulsive force due to fixed charges is reduced, thereby contributing to a decrease in cell volume (18). The cell volume decrease, reflected in the decrease in the ratio of F-actin to G-actin, in turn activates a flufenamic acid-sensitive shrinkage-activated nonselective cation channel (SANSCC) in the basolateral membrane of the taste cells. As illustrated in Fig. 2B, once activated a depolarizing current of monovalent cations flows through the SANSCCs, yielding the
receptor potential that is the basis for the phasic component of the chorda tympani response to acidic stimuli. In support of this mechanism, complete elimination of the phasic response is achieved by disrupting the transformation of F-actin to G-actin (18). For example, complete elimination of the phasic response is obtained by pretreatment of the rat tongue with cytochalasin B. The latter causes a gradual decline in F-actin and an increase in G-actin that decouples changes in cell volume from changes in pH. The consequence is complete suppression of the phasic response. The fact that the tonic phase is unaffected indicates that it has a separate mechanistic origin. The phasic component can be restored by then treating the rat tongue with phalloidin, which binds to F-actin and, therefore, stabilizes the cytoskeleton (18). Recording the HCl phasic response under voltage-clamp conditions suggests that SANSCCs are located on the basolateral membranes of taste cells. In accordance with the proposed basic phasic response mechanism, blocking SANSCC with phalloidin acid also suppresses the phasic response while leaving the tonic response intact (see Fig. 2B) (18).

Sour Tonic Response and Adaptation

Studies on isolated taste buds have shown that in a subset of taste receptor cells an acid induced decrease in pH is followed by an increase in intracellular Ca$^{2+}$ concentration (12, 19). These results suggest a role for Ca$^{2+}$ in sour transduction (see Fig. 2C). From complementary in vivo studies, records of the rat chorda tympani response to acids help to clarify the role of Ca$^{2+}$ in sour taste transduction. In experiments in which we topically applied BAPTA-AM to the rat tongue for 30 min, we obtained a response in which the phasic component was left intact, whereas the tonic phase was completely suppressed (18). We conclude that the role of Ca$^{2+}$ in sour transduction is limited to the later or tonic part of the response because intracellular Ca$^{2+}$ chelation had no effect on the phasic response whereas it essentially eliminated the tonic response. Although an increase in cell Ca$^{2+}$ concentration appears necessary to sustain the tonic sour response, we have shown that Ca$^{2+}$ also acts as a key control intermediate in the cellular mechanism of sour taste adaptation.

As illustrated in Fig. 2C, an increase in taste cell Ca$^{2+}$ subsequent to an acid-induced decrease in pH$_{t}$ activates a basolateral membrane Na$^{+}$-H$^{+}$ exchanger isoform 1 (NHE1) (13, 24). This partially restores both taste cell volume and pH$_{t}$. The net effect is the establishment of a pseudo-steady-state level of pH$_{t}$, which is determined by a balance between acid equivalents entering the sour-sensing cells from the apical side and acid equivalents exiting through NHE1 from the basolateral side. The actual level of pH$_{t}$ thereby achieved determines the sour taste adaptation level observed. The partial restoration of taste cell volume, achieved through the activation of NHE1, also reestablishes the initial conditions necessary for a subsequent phasic response should the stimulus concentration be increased. To prove that Ca$^{2+}$-activated NHE1 represents the molecular basis of taste cell sour taste adaptation we observed that increasing taste cell intracellular Ca$^{2+}$ in vivo by lingual application of ionomycin + Ca$^{2+}$ increased the level of neural adaptation (decreased the tonic response level) to an acid stimulus (13). Consistent with measurements of NHE1 activity by pH imaging, using isolated polarized fungiform papilla taste buds, the adaptation level could be restored to control level in the presence of increased cell Ca$^{2+}$ by topical lingual application of the specific NHE1 blocker, zonisamide (see Fig. 2) (13).

As summarized in Fig. 2, the sour response begins with a decrease in pH, for weak and strong acids alike. This causes a shift in the cytoskeletal F-actin to G-actin equilibrium in the G-actin direction resulting in cell shrinkage. This, in turn, activates SANSCCs that result in cell depolarization, leading to the phasic neural response. The mode by which these channels subsequently inactivate is presently unknown, but it seems that neither channel activation nor inactivation during phasic events is affected by changes in cell Ca$^{2+}$. An increase in cell Ca$^{2+}$ is, however, necessary to sustain the tonic sour response. Ca$^{2+}$ controls the activity of NHE1, which, in the continued presence of an acidic stimulus, sets the steady or adaptation level of the sour response. The fact that the sour taste phasic and tonic neural responses derive from different cellular transduction mechanisms was unexpected. However, given that reality, there is no reason to assume that it should apply uniquely to the sour modality. Accordingly, we should not be surprised to find that other taste modalities may also have separate cellular mechanisms corresponding to their phasic and tonic neural responses. The amiloride-insensitive NaCl response may be another case because a truncated phasic response to NaCl + benzamil is still observed with TRPV1 knockout mice, which otherwise give no tonic response to NaCl + benzamil.

In addition to sweeteners, salt is often added to acidic foods and beverages to improve their palatability. We generally perceive a decrease in the saltiness of food when mixed with acid. At least part of this salt-acid mixture interaction occurs at the level of the receptor cells because ENaC and TRPV1 are modulated, respectively, by intracellular and extracellular pH. In the case of ENaC a decrease in taste receptor cell pH inhibits Na$^{+}$ influx through ENaC whereas intracellular alkalization increases Na$^{+}$ influx. Accordingly, the magnitude of the chorda tympani response to NaCl is enhanced at alkaline pH and inhibited at acidic pH, i.e., in mixtures of NaCl with weak organic acids (15). Similarly, the modulation of TRPV1 activity by an agonist is strongly dependent on extracellular pH, and the activation curve is bell shaped. Most agonists activate TRPV1 maximally around pH 6.1, and the magnitude of the activation is attenuated when pH is either decreased below pH 5.5 or increased above pH 7.0 (17). Although sour is a distinct taste quality, it is also clear that the high chemical reactivity of protons in acidic foods can shape the perception of the other taste modalities by modulating cellular processes connected with their transduction and adaptation mechanisms. As the details of these mechanisms emerge so will also the corresponding proton-modulation sites.

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