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The taste of table salt

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Introduction

It is commonly held that there are five basic tastes—sweet, sour, bitter, umami (savory) and salty. Common table salt (NaCl) is perceived as “salty”, of course, yet dilute solutions also elicit sourness, sweetness, and bitterness under certain situations [4]. This is a troubling phenomenon because so-called basic tastes, by definition, should have a unique molecular and cellular mechanism for their sensory reception. There should be no confusion among the sensations when a “pure” stimulus for a basic taste, such as NaCl for saltiness, is presented. The fact is, precisely how NaCl stimulates taste buds still today remains somewhat of a mystery; the cellular and molecular mechanisms are not yet completely understood. The following pages review our current understanding of the taste of table salt. I speculate that though there may be distinct transduction mechanisms for Na⁺ at the level of taste receptor cells, taste confusions may arise after these initial events as taste buds process the information. Cells within taste buds interact synaptically and shape the final output signals that are transmitted to the primary gustatory sensory afferent fibers. These synaptic interactions may contribute to the multiple taste qualities evoked by NaCl.

Researchers studying the gustatory effects of NaCl have concluded that the cation, the anion, and the water of hydration may all contribute to the taste of this salt [3, 5]. For instance “salty” was ascribed to the Na⁺ ion, and “sweetness” to the shell of water surrounding NaCl. However, the focus of the following brief overview is on Na⁺ transduction and salty taste. Whether and how the anion or the water of hydration in NaCl solutions stimulate taste cells is another matter.

In search of how Na⁺ stimulates taste cells

Axons in the nerve that innervates the anterior tongue (*Chorda tympani*) and the posterior tongue (Glossopharyngeal) are excited by superfusing the tongue with saline solutions. Among the earliest recordings of NaCl-evoked excitation in gustatory peripheral nerves are those of Zotterman from glossopharyngeal nerve fibers in the cat [33] and Pumphrey from single axons in the frog IX nerve [22]. Those reports were followed a few years later by work from Carl Pfaffman, who studied evoked activity in chorda tympani nerve fibers when solutions of NaCl were perfused over the cat tongue [21] (Fig 1). Common to these early reports were the observations that NaCl solutions applied to the tongue evoked nerve fiber activity with a very brief latency and that an initial burst of impulses was followed by a sustained response that could be maintained for 10's of seconds. In his seminal paper of 1953, Beidler [5] set out to construct a quantitative analysis of NaCl-evoked responses by

integrating summed impulse activity recorded from the chorda tympani nerve in rats, in contrast to the single fiber recordings that had carried out previously (Fig. 2). His recordings quantified several important characteristics of NaCl-evoked taste responses, notably that the latency for onset of the nerve responses was indeed quite brief for NaCl solutions, about 50 msec. This brief latency was especially striking when compared with responses to sugar solutions. Moreover, an initial burst of nerve impulse activity preceded a sustained tonic response. Lastly, Na⁺ salts other than NaCl generated somewhat smaller nerve responses. Importantly, Beidler established detailed concentration-response relations that allowed him to generate a quantitative description of how Na salts interact with taste cells [6]. The details of NaCl-evoked responses, i.e., that they (a) had such a brief latency; (b) were relatively unaffected by temperature; (c) fit an equation similar to the Langmuir isotherm describing how molecules absorb onto a surface; and (d) generated a relatively small change in free energy (ΔF) led Beidler to conclude that Na⁺ ions bound to a surface molecule to generate a taste response. Beidler surmised “enzymatic reactions are probably not directly involved in the initial steps of taste receptor stimulation by sodium salts” [6]. In today’s parlance, this might be restated as Na⁺ ions interact with membrane channels rather than initiate a G protein-coupled pathway involving downstream effector enzymes.

Parenthetically, it should be noted that Beidler’s method of integrating electrical signals from the whole nerve de-emphasized the phasic contribution of responses, that is, the initial NaCl-evoked burst of nerve activity. His concentration-response data, and hence his conclusions regarding Na⁺ transduction, were based mainly on measurements of the sustained tonic nerve responses, a procedure that has for the most part been replicated in subsequent analyses of gustatory nerve recordings. This procedural method may have important consequences when comparing taste behavior (such as brief-access taste tests) with electrophysiological recordings. Rodents and humans can distinguish taste stimuli in under 1 sec after presentation [11, 13]. This interval is within the time frame of the rapid, phasic portion of salt-evoked nerve responses. In contrast, it has long been known that maintained taste stimulation, especially for NaCl, leads to reduced responsiveness [10] and to perceptual adaption [1]. In short, there has been a longstanding discrepancy between what has been quantified in many electrophysiological recordings from gustatory nerves and what has been measured by behavioral taste assays.

A first hint: ENaC channels are involved in Na⁺ taste

A tremendous leap in our understanding of Na⁺ taste came when John DeSimone and his colleagues showed that the sodium channel blocker, amiloride, significantly diminished chorda tympani nerve responses to NaCl solutions applied to the tongue [12] (Fig. 3).

Amiloride is a diuretic that blocks epithelial Na channels (ENaC) in the kidney. These findings strongly supported Beidler’s inference that there was some sort of membrane surface channel responsible, in part, for transducing Na⁺ salts. Human psychophysical testing had indicated that amiloride, applied topically onto the tongue, reduces the intensity of salty taste [25], but the drug also lessened sweet taste. Furthermore, subsequent investigations even challenged the notion that amiloride specifically blocked the saltiness of saline solutions. Instead, topical amiloride appeared to lessen the perception of sourness that

is commonly associated with saline solutions [20]. Further complicating the understanding of salt taste transduction was that NaCl responses in nerve recordings from experimental animals showed a significant portion of the response was not sensitive to amiloride. There appear to be amiloride-sensitive, and amiloride-insensitive components to salt taste.

Soon after, patch clamp recordings from isolated frog taste bud cells verified the presence of a stationary, inward Na^+ current that was inhibited by amiloride ($K_i \sim 0.3 \mu\text{M}$), properties consistent with, but not proving the involvement of ENaC channels [2], at least in so-called amiloride-sensitive taste (Fig 4). Intracellular impalements of rat taste cells published at the same time indicated NaCl stimulation elicited an inward current, also consistent with but not proving transduction by a Na-permeant channel such as ENaC [27].

Somewhat later, Kretz *et al* [14] used RT-PCR to show that subunits of ENaC channel that are required for a functional, amiloride-sensitive Na channel— α , β , and γ ENaC subunits—are expressed in rat taste buds on the anterior tongue (fungiform taste buds) where amiloride-sensitive salt taste is prominent (Fig. 5). Taste buds on the posterior tongue (valate taste buds) showed significantly lower expression of ENaC β and γ subunits, in good agreement with findings that salt responses in the posterior tongue are less affected by amiloride. Subsequent immunostaining for the three ENaC subunits supported these findings [16]. Thus, the regional distribution of ENaC subunits was consistent with to the topography of amiloride-sensitive versus amiloride-insensitive salt taste.

The case for ENaC channels being expressed on the tips of taste bud cells located on the anterior tongue and transducing amiloride-sensitive taste was strengthened by reports by Yoshida *et al* [32]. That group developed a novel method for recording activity in single fungiform (anterior tongue) taste buds where taste stimuli and pharmacological agents could be applied specifically to the taste pore (the route for taste stimulation in the oral cavity) versus to the basolateral cell surface. *In situ* taste cell bodies (*i.e.*, basolateral surfaces) are bathed in a constant milieu of interstitial fluid. They reported that apically-applied amiloride rapidly and reversibly blocked NaCl-evoked excitation of taste buds but basolateral application of the ENaC blocker had no effect on NaCl-evoked responses [32] but see [18] (Fig. 6). They also verified the expression of α , β , and γ ENaC subunits in salt-sensitive fungiform taste bud cells.

Consistent with these reports, genetically-engineered mice lacking ENaC α subunits in taste bud cells failed to exhibit amiloride-sensitive salt taste responses [7].

In sum, the data strongly implicate that cells in the mammalian taste bud employ ENaC channels for transducing a portion of Na^+ taste, specifically amiloride-sensitive salt responses. The mechanism(s) underlying the remaining, amiloride-insensitive salt taste remains undefined. Attempts to explain amiloride-insensitive salt transduction by invoking TRPV1-like channels [17] have not met with great success. Specifically, mice lacking TRPV1 channels (TRPV1 knockout mice) have fairly normal salt taste [24, 28].

Which taste bud cells sense Na salts?

In addition to identifying how amiloride-insensitive salt taste is transduced, what also remains to be established is the specific types of taste bud cells that express ENaC transduction channels and what is(are) the transduction pathway(s) for salt taste that is insensitive to amiloride. Taste buds consist of a population of at least 3 distinct types of cells whose functions are presently being resolved [8]. The most abundant type of taste bud cell, Type I taste cells, appears to be some sort of supporting, or glial-like cell. Electron microscopy, single cell PCR, and immunohistochemistry have shown that Type I cells express proteins associated with neurotransmitter uptake/degradation, spatial buffering of potassium ions, and anatomical segregation of cells within a taste bud. In contrast, Type II cells express G protein-coupled receptors and their downstream effectors for sweet, bitter, and umami (savory) taste. Thus, these cells have also been named Receptor cells. Type III cells sense acids (sour) but also participate in taste transduction by virtue of cell-cell synaptic interactions during taste stimulation. As mentioned, the cells responsible for sweet, bitter, umami, and sour tastes have been identified but the cellular basis for salt taste remains unresolved. Tomchik *et al* [26] showed that Type III cells respond to NaCl stimulation but amiloride sensitivity was not tested in that study (Fig. 7).

Recent studies on isolated taste bud cells also indicate that Type III taste cells transduce salt taste, at least for amiloride-insensitive responses [15]. In addition, There are claims that Type I cells mediate amiloride-sensitive salt taste [29]. Lastly, ENaC expression has been resolved in cells that were otherwise unidentified [7]. A notion that was recently put forward but that remains to be universally accepted is that amiloride-insensitive salt taste is transduced by bitter- or sour-sensing taste bud cells, corresponding to Type II (Receptor) and Type III cells, respectively [19]. In brief, all three types of taste bud cells have been implicated in transducing salt taste.

The challenge for defining unambiguously which taste cell type(s) is(are) Na⁺-sensitive, is that it is difficult to isolate, stimulate, and identify individual taste cells that respond to Na⁺ salts. Cells in isolation are bathed in physiological buffers that typically contain a significant concentration of NaCl (e.g., 140 mM), well above taste threshold concentration. Moreover, in isolated taste cell preparations, the entire taste bud cell surface, not just the chemosensitive apical tip, is exposed to taste stimulus solutions. Further, stimulating isolated cells with NaCl above ~140 mM risks osmotic shifts. Lastly, merely bathing isolated cells in a Na⁺-rich environment elicits self-inhibition of amiloride-sensitive Na⁺ channels, a form of adaptation to Na⁺ stimulation [10].

Attempts to overcome these problems, such as recording activity from isolated taste cells bathed in buffers made up with inert cations substituted for Na⁺, have partially resolved the dilemma [15]. Another approach has been to record Na⁺-evoked responses in a more intact environment than isolated cells, utilizing an imaginative micro-Ussing chamber-like approach [31]. In this methodology, individual taste buds are positioned against a flat surface having a small opening against which the taste pore abuts. In this manner, cell bodies (i.e., basolateral surfaces) of taste cells are bathed in buffer that mimics interstitial fluid while the apical chemosensitive tips of taste cells can be stimulated with increasing

concentrations of NaCl solutions. Among the important findings from this latter approach is that amiloride-sensitivity is limited to the apical tips of taste cells, not the basolateral membrane [32] but see [18]. The significance of this observation is that ENaC channels responsible for Na transduction are likely limited to the apical tips of salt-sensing taste cells and not distributed over the entire cell surface. Further, single cell PCR on RNA extracted from salt-sensitive cells in these experiments confirmed the presence of ENaC α and to a lesser extent, ENaC β and γ subunits. Importantly, Yoshida *et al* [32] did not find ENaC subunits in taste cells with amiloride-insensitive NaCl responses. Nonetheless, salt-responding cells have yet to be classified as to their taste cell types. A definitive resolution to the question of the cellular basis for salt taste remains to be found.

Why does NaCl stimulate sweet, sour, and bitter tastes?

At the outset, I mentioned that NaCl solutions elicit tastes other than saltiness. As stated, one explanation is that the water of hydration surrounding Na^+ ions contributes to the sweet taste of saline solutions [3]. Another possibility is that Na^+ stimulates the sodium-dependent glucose transporter, SGLT1, that is expressed in sweet-sensing taste cells and that may play a role in transducing sugars [30]. Explanations for other tastes of saline include that Na^+ , especially at high concentrations, stimulates sour- and bitter-sensing taste cells via unidentified mechanisms not involving ENaC channels [19]. Finally, Na^+ -sensitive taste receptor cells may interact synaptically with other receptor cells in the taste bud and thus indirectly contribute to the excitation of sweet-, bitter- or sour-sensing cells during salt stimulation. Cell-cell interactions, both excitatory and inhibitory, are known to take place during taste stimulation [8, 9, 23]. How these intragemmal cell-cell interactions shape the output of signals from taste buds during gustatory stimulation remains uncertain. Nonetheless, synaptic interactions between taste cells during NaCl stimulation may contribute to taste confusion and to the side tastes of salt.

Summary

Table salt elicits saltiness, likely via multiple transduction mechanisms. Early recordings from gustatory sensory nerves identified responses to lingual stimulation with NaCl. Those data were interpreted as indicating an interaction of Na^+ ions with a surface-bound molecule on taste cells. That surface molecule has eventually been identified as an epithelial sodium channel, ENaC. Interestingly, ENaC channels are key to how kidneys maintain the body's Na^+ homeostasis, thereby linking salt taste to renal function. Transduction mechanisms other than ENaC channels exist but remain unknown, as are the identities of the specific types of cells in the taste bud that respond to salt stimulation.

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Figure 1. Early recordings of single fiber impulses from gustatory nerves in response to salt stimulation

A, action potentials from a salt-responsive axon in glossopharyngeal nerve of the frog when the tongue was stimulated with ~350 mM NaCl. Modified from Pumphrey [22]. **B**, impulses from gustatory nerve in the cat (chorda tympani or glossopharyngeal was not specified) elicited by 500 mM NaCl applied to the tongue. Modified from Pfaffman [21]. A and B are among the first published records of gustatory nerve responses evoked by salt solutions.

Figure 2. Chorda tympani nerve responses in the rat elicited by stimulating the tongue with NaCl

A, activity measured from the whole nerve in response to lingual application of 0.2 M NaCl for 10 sec. Calib, 200 msec. **B**, integrated activity of nerve responses as in B, evoked by increasing concentrations of NaCl, from 5 mM to 1 M, applied for 7–10 sec. Calib, 20 sec. **C**, concentration-response relations from integrated whole chorda tympani nerve recordings as in B. Modified and re-plotted from Beidler [5].

Figure 3. Affect of amiloride on NaCl-evoked taste responses

A, Integrated chorda tympani nerve response in rat, elicited by 1 M NaCl applied to the tongue before (a) and after (b) five minute exposure to 100 μ M amiloride. Calib, 30 sec. **B**, concentration-response relations for NaCl taste stimulation in the absence ($\circ$) and presence ($\bullet$) of 100 μ M amiloride. Modified and replotted from Heck *et al.* [12].

Figure 4. Amiloride blocks inward Na^+ current in frog taste bud cells

Patch clamp recording from an isolated taste bud cell from frog tongue. The cell was held at -23 mV, resulting in a sustained inward current that was reversibly blocked by adding 30 μM amiloride to the bathing solution. Calib, 2 min. Modified from Avenet and Lindemann [2].

Figure 5. ENaC α , β , and γ subunits are expressed in taste buds

The figure shows mRNAs found by RT-PCR in pools of rat taste bud cells. α , β , and γ ENaC subunits are expressed in taste buds from the anterior tongue (fungiform, F). Taste buds in the posterior tongue (vallate, V) lack β and γ ENaC subunits. α -Gustducin, a taste-specific G protein, was found primarily in vallate taste buds (bottom panel). Neg, negative control; pos, positive control. From Kretz *et al.* [14].

Figure 6. NaCl-evoked responses in taste buds are blocked by amiloride that is applied to the apical, but not basolateral membrane of taste buds

A,B, diagram and micrograph, respectively, of apparatus for recording electrical activity from single taste bud cells. In this apparatus, taste buds have their taste pore open to, and thus apical tips immersed in a separate bathing solution from their cell bodies (*i.e.*, basolateral membranes). from Yoshida *et al* [31]. **C**, NaCl-evoked responses recorded from a mouse taste cell. NaCl was applied to the apical tip in the absence of amiloride (a), or with 30 μ M amiloride present in the apical solution (b) or in the basolateral solution (c). Only apically-applied amiloride blocks NaCl-evoked responses. Modified from Yoshida *et al* [32].

Figure 7. NaCl stimulation elicits responses in Type III taste bud cells

A–C, micrographs of a taste bud in a lingual slice prepared from a transgenic mouse that expressed GFP in Type III cells (taste cells that express GAD1) and in which taste buds had been injected with the fluorescent, calcium-sensitive dye, Calcium Orange (CaO).

Arrowhead points to one cell that expresses GFP (i.e. is a Type III cell) and which also is loaded with CaO. D, focal application of taste stimuli onto the taste pore evoked responses (& fluorescence, representing $[Ca^{2+}]_i$) in the Type III cell marked with an arrowhead in A–C. Note, NaCl, as well as certain other taste compounds stimulate Type III cells. cit, 100 mM citric acid (sour); cyx, 30 μ M cycloheximide (bitter); suc, 500 mM sucrose (sweet); MPG, 200 mM monopotassium L-glutamate plus 1 mM IMP (umami); den, 200 μ M denatonium (bitter); SC4, 100 μ M SC45647 (a high potency synthetic sweetener); 500 mM NaCl (salty). Modified from Tomchik *et al* [26].