Minireview
Why do taste cells generate action potentials?
Aurelie Vandenbeuch and Sue C Kinnamon

Address: Department of Otolaryngology and Rocky Mountain Taste and Smell Center, 12700 E. 19th Ave, Aurora, CO 80045, USA.

Correspondence: Sue C Kinnamon. Email: sue.kinnamon@ucdenver.edu

Abstract

Taste cells regularly generate action potentials, but their functional significance in taste signaling is unclear. A paper in *BMC Neuroscience* reveals the identity of the voltage-gated Na$^+$ channels underlying action potentials, providing the foundation for insights into their function.

More than two decades ago, Steve Roper first reported that the large taste cells of the aquatic salamander *Necturus* are electrically excitable and generate action potentials in response to membrane depolarization [1]. It is now well documented that the taste cells of most, if not all, vertebrate species regularly generate action potentials not only on electrical stimulation, but also in response to apically applied chemical stimuli. But why should taste cells, which are short receptor cells lacking axons, require action potentials to activate gustatory afferent nerve fibers? Graded receptor potentials are sufficient to evoke transmitter release from other 'short' sensory receptor cells, such as hair cells and photoreceptors. In fact, taste cells appear to be the only non-neuronal sensory receptor cells to generate action potentials.

Although the physiological significance of action potentials in taste transduction is still unclear, a new report by Gao *et al*. in *BMC Neuroscience* [2] provides the molecular substrates to address this important question. They have identified three genes that encode the tetrodotoxin (TTX)-sensitive Na$^+$ currents that underlie the action potential in taste cells. These include SCN2A (Nav1.2), a common neuronal isoform, SCN3A (Nav1.3), an isoform typically expressed in immature neurons, and SCN9A (Nav1.7), an

isoform expressed primarily in pain fibers. These isoforms are expressed selectively in particular taste cell types and the expression pattern of each provides insights into their role in taste signaling.

Action potentials and voltage-gated currents in taste cells

Taste cells are primary receptor cells that are derived from local epithelium rather than from neuronal precursors [3]. Yet, many taste cells possess electrical properties similar to neurons and are capable of firing action potentials either spontaneously or in response to electrical or chemical stimulation. Properties of the voltage-gated currents in rodent taste cells have been characterized by whole-cell recording in a number of laboratories [4-7]. Both voltage-gated Na$^+$ and Ca^{2+} currents participate in the depolarizing phase of the action potential of taste cells, while K$^+$ and, possibly, Cl$^-$ currents elicit the repolarization phase. All voltage-gated Na$^+$ currents in taste cells are TTX-sensitive. Potassium currents inactivate slowly and are inhibited by tetraethylammonium, Ba^{2+}, and, in some cells, 4-amino-pyridine. Both high-voltage-activated and low-voltage-activated Ca^{2+} currents have been reported in subsets of taste cells. Recent studies using transgenic mice expressing

green fluorescent protein in selected taste cell types show that these currents are expressed differentially in functional subsets of taste cells, as described below.

Three types of taste cells are present in each taste bud (see [8] for a recent review). Type I cells are generally believed to have a support function in the taste bud, similar to astrocytes in the nervous system. These cells express primarily voltage-gated outward currents and thus are incapable of generating action potentials. Type II cells, also called 'receptor' cells, possess the G-protein-coupled receptors and downstream signaling effectors for bitter, sweet, and umami taste. In these cells, receptor binding initiates a transduction cascade involving activation of phospholipase Cβ2, release of Ca^{2+} from intracellular stores, Ca^{2+}-dependent activation of the monovalent-selective cation channel TRPM5, membrane depolarization, and release of transmitter. Type III taste cells, also called 'synaptic cells' because they have prominent synapses with afferent nerve fibers, respond to acids, which elicit sour taste. The nonselective cation channel PKD2L1 is expressed exclusively in type III cells, where it has been hypothesized as the sour receptor; however, confirmation of a role in sour transduction awaits genetic knockout. Both type II and type III taste cells are electrically excitable, but the Na^+ channel isoforms that are expressed differ between the two cell types. Gao *et al*. [2] establish that type II taste cells express SCN2A, SCN3A and SCN9A, whereas type III cells express only SCN2A. These differences in subunit expression suggest differences in function for the channels in type II and type III cells.

Various studies have demonstrated that both type II and type III taste cells generate trains of action potentials in response to taste stimuli. These studies include whole-cell recording [9], loose-patch recording from the taste pore of taste buds *in situ* [10], and loose-patch recording from single taste cells in taste buds [11]. However, type II and type III cells display differences in the magnitude and kinetics of their underlying voltage-gated currents, as illustrated in Figure 1a. Although type II cells tend to be larger than type III, as estimated by membrane capacitance, the magnitude of both the inward Na^+ current and the outward K^+ current is substantially smaller in type II cells compared to type III. Furthermore, the K^+ current in type III cells activates more rapidly and shows a fast inactivating component, unlike that of type II. As might be predicted from their underlying currents, the duration of the action potential in type II taste cells is longer than in type III cells, and type II cells are generally less excitable than type III [4,6].
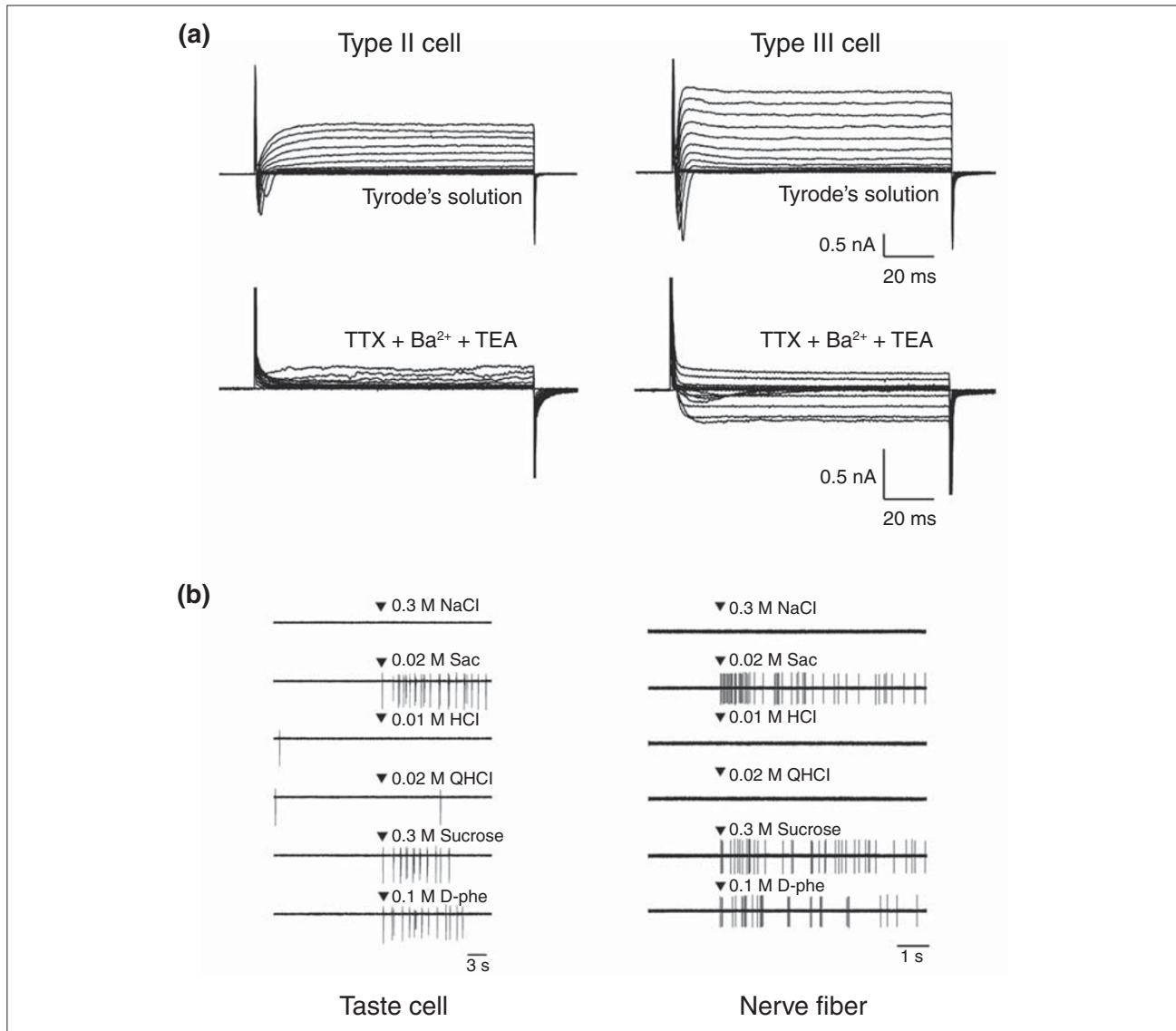
However, the most striking difference between type II and type III taste cells is the apparent lack of voltage-gated Ca^{2+} channels in type II taste cells, as reviewed in [8]. Type II cells

lack not only voltage-gated Ca^{2+} currents, but also the presynaptic machinery normally associated with conventional synapses. Type II cells release ATP via gap-junction hemichannels to activate purinergic receptors on afferent nerve fibers [12,13]. Release can be evoked by bitter taste stimulation [12] or by membrane depolarization, even in the complete absence of Ca^{2+} [13]. The identity of the hemichannel(s) responsible for ATP release is still somewhat controversial, although both pannexin-1 and several connexins are expressed in type II taste cells and are viable candidates. In contrast to type II cells, type III cells exhibit prominent voltage-gated Ca^{2+} currents, and show Ca^{2+}-dependent release of serotonin (5-HT) and norepinephrine on membrane depolarization [14]. However, the role of these biogenic amines in taste signaling is not yet clear.

Possible roles of action potentials in taste cells

Several roles for action potentials in taste signaling have been proposed. First, action potentials probably facilitate transmitter release, for both ATP and 5-HT, although by different mechanisms. ATP release relies on Ca^{2+} release from intracellular stores and subsequent Ca^{2+}-dependent activation of TRPM5 to depolarize taste cells. The resulting activation of voltage-gated Na^+ channels boosts the graded depolarization produced by TRPM5 to the high voltage threshold required for gating the gap-junction hemichannels. Romanov *et al*. [13] have shown that depolarization in excess of +10 mV (that is, 50-75 mV depolarized relative to resting potential) is required to evoke ATP release from type II cells, suggesting that action potentials may be required for ATP release. Patch-clamp studies show that TRPM5 in taste cells desensitizes rapidly [15], so the prolonged action potentials of type II taste cells may offer a mechanism for increasing the open time of the hemichannels regulating ATP release. Type III taste cell behavior is more similar to that of neurons. In these cells, as in neurons, action potentials can activate the voltage-gated Ca^{2+} channels required for vesicular release of 5-HT and norepinephrine. Nonetheless, in both types of taste cells action potentials may be required for activation of gustatory afferent nerve fibers.
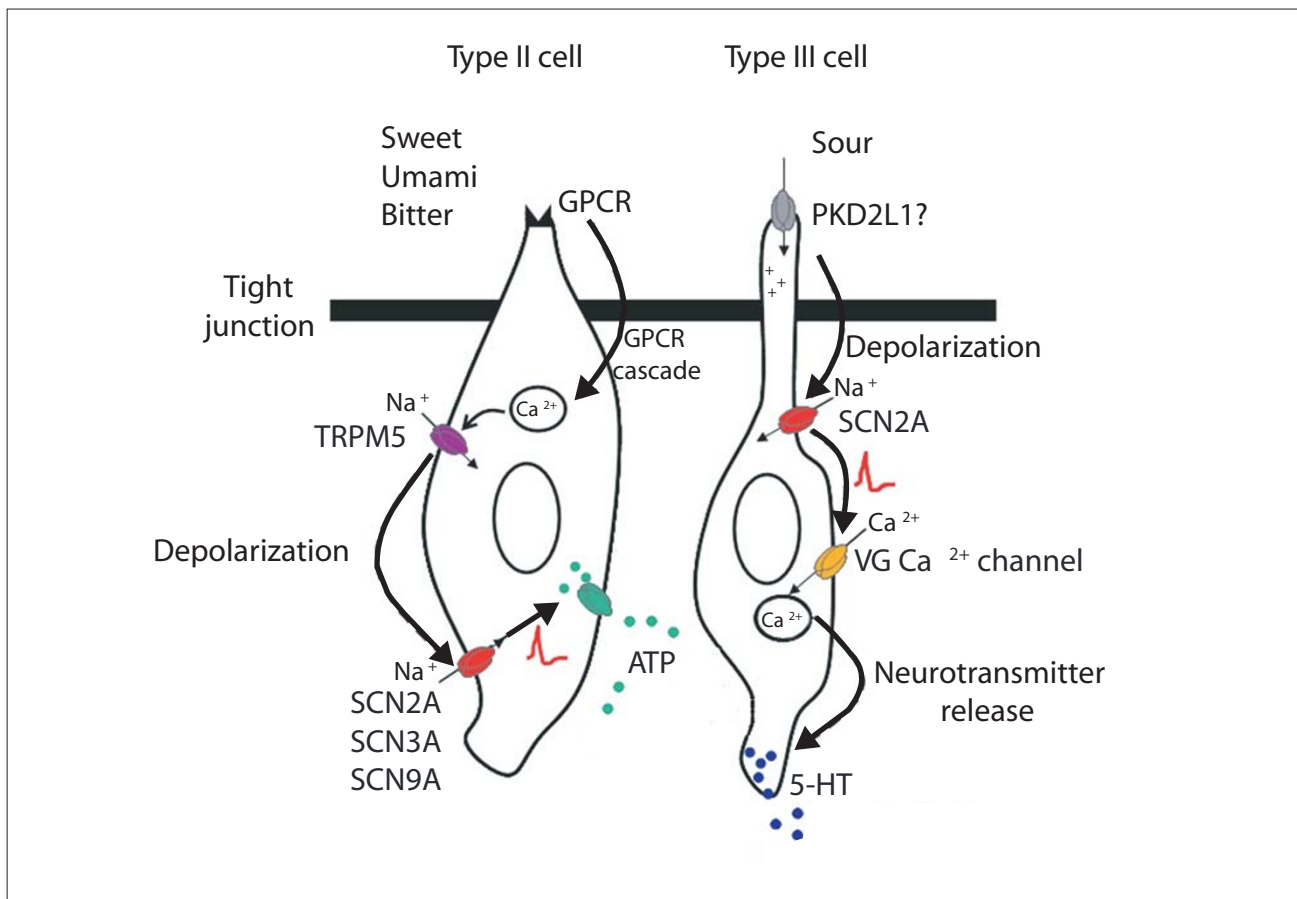
How do the Na^+ channel isoforms expressed relate to the function of each cell type? The two isoforms that are expressed exclusively in type II taste cells are SCN3A and SCN9A. SCN3A is primarily expressed in developing neurons, as explained by Gao *et al*. [2]. Taste cells are continuously turning over, and recent studies suggest that type III cells may have a longer life span than type II [16]. Thus, the expression of SCN3A in some type II cells may correlate with their relative state of immaturity, but further studies will be required to substantiate this. Outside the taste system, SCN9A

Figure 1

Electrophysiological properties of taste cells. **(a)** Type II (left panel) and type III (right panel) taste cells show discrepancies in their voltage-gated currents. Type II taste cells exhibit a smaller inward Na^+ current and a slowly activating K^+ current compared with type III cells. Only type III cells exhibit a voltage-gated Ca^{2+} current, as revealed by inward currents in the presence of Ba^{2+}. Holding potential -70mV (AV and SCK, unpublished). TEA, tetraethylammonium; TTX, tetrodotoxin. **(b)** When the apical region of a taste bud is stimulated with various tastants, the action-potential firing pattern in single taste cells (left panel) resembles the pattern in single chorda tympani nerve fibers (right panel). The breadth of tuning in the taste cell is nearly identical to that in the nerve fiber, suggesting that coding may begin at the level of the taste cell and require action potentials [11]. D-phe, D-phenylalanine; QHCl, quinine-HCl; Sac, sodium saccharin.

is predominately expressed in pain fibers. One of the characteristic features of this channel is its slow inactivation compared with other voltage-gated Na^+ channels [17]. Type II cell Na^+ currents do inactivate more slowly than type III cell currents and SCN9A may be responsible for this. As mentioned above, the longer-duration Na^+ currents may permit a more prolonged release of ATP.

Finally, the frequency of action potentials in taste cells is proportional to the intensity of the stimulus applied [11]. Moreover, the firing pattern of action potentials in taste cells may be quality-dependent. A trained neural network can distinguish action potential responses of taste cells to NaCl from responses to sucrose and other sweeteners [18]. Whether the firing pattern is involved in quality coding, or

Figure 2

Roles of voltage-gated Na$^+$ channels in taste cells. Left: sweet, bitter and umami compounds bind to G-protein-coupled receptors (GPCR) present in the apical membrane of type II taste cells. After transduction, Ca^{2+} is released from internal stores and activates TRPM5 channels (purple). Na$^+$ enters the cell, depolarizes the membrane, and activates voltage-gated Na$^+$ channels (SCN2A, SCN3A, SCN9A; red) to elicit action potentials (red trace). ATP (green dots) is then released through pannexin-1 and/or connexin-based hemichannels (green), where it presumably activates purinergic receptors on afferent nerve fibers and adjacent taste cells (omitted for simplicity). Right: in comparison, type III taste cells are depolarized by sour stimuli (protons), the depolarization possibly involving PKD2L1 channels in the apical membrane. Membrane depolarization activates voltage-gated Na$^+$ channels (SCN2A), causing action potentials (red trace) and Ca^{2+} influx via voltage-gated (VG) Ca^{2+} channels (yellow), leading to the release of 5-HT and norepinephrine (blue dots). Whether these biogenic amines activate nerve fibers or modulate adjacent taste cells has not been determined. The tight junction seals adjacent epithelial cells in a narrow band just beneath their apical surface.

simply reflects differences in the underlying Na$^+$ channel isoforms in sweet-sensitive and salt-sensitive taste cells, is not clear. Similarities have been observed in the firing of taste cells and afferent nerve fibers, especially regarding their breadth of tuning (Figure 1b) [11]. Thus, coding probably begins at the level of the taste cell and may require action potentials.

The potential roles of the newly discovered Na$^+$ channel isoforms are summarized in the model shown in Figure 2. Although the functional significance of action potentials in taste cells remains unclear, knowing the identity of underlying voltage-gated Na$^+$ channels will allow the role of

each channel to be defined in terms of the various functions that have been proposed. Molecular substrates are now in place to begin addressing the important question of why taste cells generate action potentials.

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