COMMENTARY

Sour taste finds closure in a potassium channel

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Taste cells in taste buds of the mammalian tongue and oral cavity can detect five basic modalities: sweet, bitter, umami, salty, and sour. Each taste cell expresses distinct molecular sensors, such as G protein-coupled receptors or ion channels, which detect tastants (i.e., chemical stimuli that elicit taste sensation) and initiate an intracellular response that culminates in membrane depolarization and/or action potentials (APs) causing transmitter release. The race to solve the molecular identity of taste receptors more than 20 y ago sparked a revolution in gustatory physiology. The transduction components for sweet, bitter, umami, and salty taste have since been documented (1, 2), but sour taste remains poorly understood. The sour taste machinery has begun to emerge in recent years, but the intracellular response underlying sour taste detection is not known. In PNAS, Ye et al. (3) report a potassium (K^+) channel as a key component of sour taste transduction, which fills a significant gap in the field.

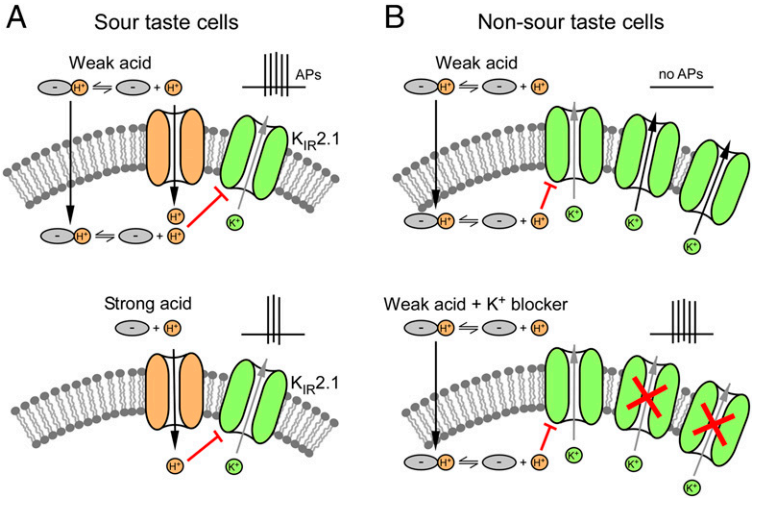

Fig. 1. Potential contribution of the $K_{IR}2.1$ channel in sour and nonsour taste cells. (*A*) In sour (PKD2L1) taste cells, weak acid causes stronger AP firing (*Upper*) than strong acid (*Lower*) at the same pH, presumably by intracellular acidification. (*B*, *Upper*) In nonsour (TRPM5) taste cells, weak acid stimulation does not cause AP firing, likely due to the large $K_{IR}2.1$ current. (*B*, *Lower*) When the $K_{IR}2.1$ current is mostly blocked, weak acid stimulation can cause AP firing.

Many ion channels have been proposed to mediate sour taste transduction, including a transient receptor potential (TRP) channel PKD2L1 and its partner PKD1L3 (4–11). Involvement of PKD family members in sour detection is supported by the fact that selective ablation of PKD2L1 cells nearly eliminates acid-induced responses in mouse gustatory nerve recordings (12). However, the functions of PKD2L1/PKD1L3 channels in sour taste remain enigmatic, given that genetic ablation of these channels has only a modest impact on acid-induced responses (13, 14). Nevertheless, PKD2L1 is a valuable molecular marker for sour cells (or type III taste cells), and its characterization has paved the way for the discovery of a Zn^{2+}-sensitive proton conductance in PDK2L1 cells, which is believed to be the initial sour taste transduction event (15).

The current consensus in the field is that upon acid stimulation (Fig. 1*A*), protons are shuttled into the cell via a proton channel, which ultimately leads to cell depolarization and the firing of APs. How the proton conductance mediates cell depolarization remains unknown, but previous studies have hinted at a potential role of cytosolic acidification in sour taste transduction. This hypothesis stems from the observation that weak acids, which can diffuse across the lipid bilayer, evoke stronger responses in the gustatory nerve compared with strong acids (at the same pH), which cannot diffuse across the cell membrane (16, 17) (Fig. 1*A*). Moreover, the proton conductance measured in sour taste cells in response to extracellular acid is likely insufficient to elicit APs on its own (18). Together, these data point to intracellular acidification as a second component of sour taste transduction. Until now, this hypothesis has not been directly tested.

Here, Ye et al. (3) tested whether intracellular acidification mediates the sour taste response. To prevent contributions from endogenous proton conductance, Zn^{2+} was used to block the proton channel in all experiments. By recording weak acid-induced responses from genetically labeled sour taste cells (PKD2L1-YFP) and nonsour taste cells (TRPM5 cells for sweet, umami, or bitter sensing), the authors found that APs are evoked in PKD2L1 cells but not in TRPM5 cells, supporting that

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only sour taste cells are sensitive to cytosolic acidification. How then does intracellular acidification generate depolarization and APs in sour taste cells? Cell depolarization may be caused by either inward Na^+ or Ca^{2+} current or inhibition of outward K^+ current. Ye et al. (3) explored each of these possibilities, including the potential role of PKD2L1, and discovered that cytosolic acidification has an exclusive impact on resting K^+ currents in PKD2L1 cells by blocking K^+ conductance. Although pH-sensitive K^+ channels are known to be expressed in the taste epithelium (9, 11), this demonstration is the first, to our knowledge, that cytosolic acidification excites sour taste cells by directly blocking the resting K^+ current.

To identify the acid-sensitive resting K^+ current, Ye et al. (3) used transcriptome analysis and pharmacological profiling, which, together, implicate $K_{IR}2.1$ as the source of the pH-sensitive K^+ conductance (Fig. 1*A*). The authors then went on to demonstrate that heterologous expression of $K_{IR}2.1$ confers sensitivity to acids, and that tissue-specific ablation of $K_{IR}2.1$ in PKD2L1 cells significantly reduces the magnitude of the resting K^+ current. These results strongly suggest that $K_{IR}2.1$ functions to amplify the sensory response to sour taste stimuli.

Surprisingly, $K_{IR}2.1$ is not only expressed in sour taste cells but also in TRPM5 cells. Why does cytosolic acidification evoke APs in sour taste cells but not in nonsour taste cells, even though both cell types express $K_{IR}2.1$? To answer this question, Ye et al. (3) compared the magnitude of the resting K^+ current in PKD2L1 and TRPM5 cells. Intriguingly, TRPM5 cells exhibit much larger K^+ currents compared with PKD2L1 cells, presumably due to a greater density of $K_{IR}2.1$ channels on the cell surface (Fig. 1*B*). This larger outward K^+ current renders nonsour taste cells insensitive to intracellular acidification because more $K_{IR}2.1$ channels would need to be closed to depolarize the cell and elicit a response. Surely enough, the authors show that when the magnitude of the resting K^+ currents is reduced in nonsour cells, APs are fired upon weak acid stimulation (Fig. 1*B*). These data indicate that the small magnitude of the K^+ current, rather than specific expression of $K_{IR}2.1$ itself, facilitates the sour taste response. Furthermore, because PKD2L1 cells, but not TRPM5 cells, display a Zn^{2+}-sensitive proton conductance in response to changes in cytosolic pH, the authors conclude that proton entry blocks the $K_{IR}2.1$-mediated resting K^+ current exclusively in sour taste cells. Together, Ye et al. (3) propose a mechanism for sour taste signaling in which $K_{IR}2.1$ functions downstream of proton influx to amplify the sensory response. This mechanism resembles G protein-mediated olfactory transduction in which a Ca^{2+}-activated Cl^- current amplifies the initial depolarization caused by opening of the cyclic-nucleotide gated channel (19).

This study offers a plausible explanation to the long-sought mystery of why weak acids taste sourer than strong acids (at the same pH): by cytosolic acidification and downstream inhibition of $K_{IR}2.1$. Future studies are needed to tease out the potential contributions of other ion channels reported in sour taste cells and achieve a comprehensive understanding of how these channels orchestrate sour detection under various conditions. This work also has broad implications for the function of $K_{IR}2.1$, which is ubiquitously expressed in many organs throughout the body, including the brain, heart, kidney, and muscles (20). Understanding how diverse cell types might detect and perceive acid stimuli could inform the role of acid-sensitive receptor cells outside of the taste system, further expanding our knowledge of the mammalian chemosensory repertoire.

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