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COMMENTARY

The Search for Mechanisms Underlying the Sour Taste Evoked by Acids Continues

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Abstract

It has been postulated for decades that ion channels serve as receptors for most sour tasting stimuli. Though many candidates exist, definitive evidence linking any particular channel to sour taste perception has been elusive. Several studies have suggested that two members of the polycystic kidney disease-like family may function as components of an ionotropic taste receptor mediating the transduction of acids. However, the precise role of these proteins in sour taste is controversial. In this issue of *Chemical Senses*, Nelson et al. use behavioral and electrophysiological approaches in gene-targeted mice to show that one of these putative sour taste receptor subunits, Pkd1l3, is unnecessary for normal taste responses to acids. Their results suggest that other mechanisms and/or other candidate receptors must be contributing to the transduction of acids and the subsequent perception of sour taste.

Key words: gustatory nerves, preference, Pkd1l3, receptor, transduction, threshold

Taste stimuli elicit perceptions that can be categorized into five qualities—sweet, bitter, salty, sour, and umami—each of which is associated with a biologically relevant class of compounds (Bartoshuk 1988; Breslin and Spector 2008). Although diverse compounds can taste sour, the most common sour taste stimuli are acids (Breslin and Spector 2008). Sweet, bitter, and umami tasting stimuli are recognized by G protein–coupled receptors (Zhang et al. 2003; Chandrashekar et al. 2006; Temussi 2009), but it has long been thought that ion channels serve as receptors for salts and acids (Bigiani et al. 2003). Many candidate sour taste receptors have been proposed over the years (e.g., hyperpolarization-activated channel [HCN], acid-sensitive ion channel [ASIC]; Lindemann 2001; Bigiani et al. 2003). Nevertheless, evidence definitively linking any one of these molecules to the detection of acids has been lacking. However, recent studies suggested a new group of candidate sour taste–related channels: the polycystic kidney disease-1 and -2–like proteins, Pkd1l3 and Pkd2l1 (Huang et al. 2006; Ishimaru et al. 2006; LopezJimenez et al. 2006).

Pkd2l1 and Pkd1l3 are intriguing candidates for a sour taste receptor. They combine in vitro to form an acid-sensitive channel (Ishimaru et al. 2006; Inada et al. 2008). However, these two channel proteins are not expressed uniformly throughout the oral cavity. Pkd2l1 is expressed in all three taste bud–containing papilla on the tongue, as well as in taste cells of the palate (Huang et al. 2006; Ishimaru et al. 2006). On the other hand, Pkd1l3 is expressed only in circumvallate (CV) and foliate papilla (Huang et al. 2006; Ishimaru et al. 2006; LopezJimenez et al. 2006). If the Pkd1l3/Pkd2l1 receptor mediates acid transduction, then the expression patterns of these two proteins would suggest that taste receptor cells from the CV and foliate papillae should be significantly more responsive to acids than cells in the fungiform papillae and palate. However, taste receptor cells from the fungiform papillae respond robustly to acids (Yoshida et al. 2009), as does

the chorda tympani (CT), which innervates fungiform taste buds (Ninomiya et al. 1982, 1984; Danilova and Hellekant 2003). Indeed, responses to acid tastants, in both the glossopharyngeal (GL) nerve, which innervates the CV and foliate papilla, and the CT, are practically indistinguishable (e.g., Danilova and Hellekant 2003). These data cast doubt on what functional roles Pkd1l3 and Pkd2l1 may play in sour taste perception. In this issue of *Chemical Senses*, Nelson et al. (2010) provide compelling evidence that one of these proteins, Pkd1l3, is not required for normal sour taste responses in mice.

The researchers examined taste responsiveness of both wild-type and Pkd1l3 knockout mice using behavioral and electrophysiological approaches. Behavioral preference for a large battery of tastants was measured using 48-h two bottle tests. Taste thresholds for NaCl and citric acid were determined using a novel conditioned taste aversion technique (see Ishiwatari and Bachmanov 2009 for details). Lastly, electrophysiological activity in response to stimulation with multiple taste stimuli was assessed in both the CT and GL nerves. These three groups of experiments gave similar results: Pkd1l3 knockout mice showed no significant reduction in taste responsiveness to acids relative to controls.

The behavioral preference data were particularly compelling. Despite the putative loss of neural input from the oral cavity, no effects of the loss of Pkd1l3 were observed on the suprathreshold responsiveness of mice to HCl or citric acid across a broad range of concentrations. Coupled with the electrophysiological data, this outcome indicates that the loss of Pkd1l3 did not affect the response properties of either the CT or GL nerves. This is not surprising for the CT considering that Pkd1l3 is not expressed in taste receptor cells in the fungiform papillae. However, if the Pkd1l3/Pkd2l1 receptor mediates acid transduction in the GL receptive field, then one would predict a loss of responsiveness in the absence of Pkd1l3. On the other hand, Pkd2l1 may have an unidentified partner, other than Pkd1l3, that can subserve normal taste functioning in the absence of Pkd1l3 (either by knockout or by its lack of expression in cells in fungiform papillae and in the palate). Additionally, there remains the possibility that changes in the response properties of the nerves occur only at concentrations lower than those tested in these experiments. However, it is clear that Pkd1l3 does not have a broad effect on nerve responses induced by acid tastants.

The transduction of acid stimuli by taste receptor cells may turn out to be more complex than what is seen for other taste qualities. In fact, the response properties of taste receptor cells that respond to acids vary substantially (e.g., Lin et al. 2002), suggesting that multiple, independent factors can influence their responsiveness. For example, a report by Lin et al. (2002) showed that some rodent taste receptor cells display a so-called characteristic "off-response" when acid stimuli are removed from the cells. Data from in vitro studies suggest that the Pkd1l3/Pkd2l1 receptor mediates this off-response (Inada et al. 2008). Whether or not this off-response, observed in both taste receptor cells and gustatory nerves of various rodents and primates (Danilova et al. 2002; DeSimone et al. 1995; Lin et al. 2002), is affected by the loss of Pkd1l3 in vivo is unknown (the off-response was not assessed by Nelson et al.). In any case, the loss of Pkd1l3 had no measurable impact on behavior responsiveness even if it did eliminate or significantly dampen this response. These results beg the question as to what, if any, significance do off-responses have? One possibility is that the off-response impacts upon the perceptual quality of acids but not on their detectability or hedonic valence. Be that as it may, it is clear that much more research on the nature and characteristics of the off-response is required before these responses can be linked to any type of taste-related function.

It is conceivable that factors other than Pkd2l1/Pkd1l3 are involved in sour taste perception. For example, the carbonic anhydrase isoform Car4 was recently implicated in the transduction of the sour taste of carbon dioxide (Chandrashekar et al. 2009). It has also been postulated that undissociated acids and/or H^+ ions can enter into taste receptor cells and acidify the cytoplasm, contributing to the perception of sour taste (DeSimone et al. 2001; Lyall et al. 2001). More recent data suggest, however, that although over 90% of taste receptor cells within a taste bud are acidified by the application of acid stimuli, only a few of these cells exhibited acid-evoked increases in intracellular calcium (Richter et al. 2003). These data suggest that only a select subset of cells possess the molecular machinery to transduce acid stimuli (Richter et al. 2003). Nevertheless, whether any of these factors interact with acid transduction via Pkd-mediated mechanisms to impact upon sour taste perception remains to be investigated.

In mice, the genetic ablation of taste receptor cells expressing Pkd2l1 eliminates CT responses to acid taste stimuli while leaving responsiveness to stimuli evoking the other taste modalities undisturbed (Huang et al. 2006). These results strongly suggest that Pkd2l1-expressing cells mediate our perceptions of sour taste. The generation of Pkd2l1 knockout mice will help determine if Pkd2l1 is necessary for guiding normal taste responsiveness to acids or if the protein plays some other role in sour-sensitive cells. Both extremes (i.e., complete mediation or total noninvolvement) appear to be unlikely. Indeed, data from a recent study on acid taste sensitivity in humans suggest the involvement of PKD-like receptors, as well as other receptors in the mediation of sour taste (Huque et al. 2009). In this study, the expression level of gene transcripts in taste receptor cells were compared between subjects ageusic to sour tasting stimuli and those with normal sour taste sensitivity. Various ASIC isoforms as well as the channels PKD1L3 and PKD2L1 were readily detectable in subjects with normal taste sensitivity. However, none of these transcripts were detectable in subjects with sour taste ageusia (Huque et al. 2009). Although these data are certainly not conclusive and must be interpreted with extreme caution (e.g., ageusic subjects may simply lack sour-sensitive taste cells), they hint

at the possibility that ASICs may be playing some role in sour taste perception.

In conclusion, although several lines of evidence from in vitro studies suggest that Pkd1l3/Pkd2l1 is a putative sour taste receptor, data from Nelson et al. (2010) indicate that one of the subunits, Pkd1l3, is unnecessary for normal taste related responsiveness to acids. Thus these data, together with information on the expression patterns of these proteins, implicate other mechanisms and/or other candidate receptors in the transduction of acids and the subsequent perception of sour taste. The generation and phenotyping of mutant mice lacking other candidate sour taste receptors (e.g., HCN, ASICs and Pkd2l1) will be critical in elaborating upon the seemingly complex mechanisms underlying the taste of acids in vivo.

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