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Generation and Behavioral Analysis of Knockout Mice for Multiple TRP Ion Channels

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Summary

Among five basic taste qualities, much progress has been made in studies on molecular mechanisms of sweet, bitter, and umami (savory) taste including two families of taste receptors, T1R and T2R, and the downstream signal transduction molecules in the last decade. In contrast, none of candidate receptors had been demonstrated to be required for salt or sour taste detection *in vivo*, although several candidate salt and sour taste receptors have been reported.

In electrophysiological analyses of gustatory nerves, two pharmacologically distinct components of responses, amiloride-sensitive and amiloride-insensitive, were observed upon stimulation with NaCl, suggesting at least two different mechanisms for the detection of salty tastants. Recently, it has been proved that epithelial Na^+ channels (ENaCs) function as amiloride-sensitive salt taste receptors (Chandrashekar *et al*., *Nature*, 2010). Although TRPV1t, a variant of TRPV1, has been proposed as a candidate amiloride-insensitive salt taste receptor, the role of TRPV1t in salt taste remains controversial. We have been proposed PKD1L3/PKD2L1 as a candidate sour taste receptor (Ishimaru Y *et al*., *Proc. Natl. Acad. Sci. USA*, 2006). TRPV1 is expressed in the nerve terminals of somatosensory neurons and responds to low pH, raising the possibility that TRPV1 may have a role in sour detection as a somatosensor. In this study, we attempted to clarify the role of *PKD1L3*, *PKD2L1*, and *TRPV*1 genes in taste detection including salt and sour taste using *PKD1L3*, *PKD2L1*, *TRPV*1 KO mice and *PKD2L1*/*TRPV*1 double KO mice.

We generated *PKD1L3* KO and *PKD2L1* KO mice, in which predicted pore regions which are supposed to be important for channel function are deleted. Double heterozygote mice were generated by crossing *PKD2L1* KO and commercially available *TRPV1* KO. Double KO mice were generated by crossing the double heterozygote mice. To examine the phenotype of these KO mice in taste detection including salt and sour taste, we next performed behavioral analysis such as two-bottle preference test. As a result, *PKD1L3*, *PKD2L1*, and *PKD2L1*/*TRPV1* double KO mice showed normal preference or avoidance behavior similar to the wild-type littermates for all the five basic taste qualities. In contrast, *TRPV1* KO mice consumed more 100 mM NaCl, 300 mM NaCl, and 10 mM citric acid solution than the wild-type mice. In gustatory nerve recording, both whole-nerve and single-fiber chorda tympani nerve responses of *PKD2L1* KO to sour solutions such as citric acid, HCl, and acetic acid significantly reduced compared with the wild-type mice.

Collectively, these results demonstrate that PKD2L1 functions as a sour taste receptor *in vivo* and suggest that there are multiple mechanisms underlying sour and salt taste detection such as somatosensation other than via taste buds.