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Taste Receptor Cells Share Common Pathway

Although sweet, bitter and umami (monosodium glutamate) tastes are different, researchers are finding that information about each of these tastes is transmitted from the various taste receptors via a common intracellular signaling pathway.

The identification of a common pathway runs counter to widespread belief among some researchers in the taste field who have long held the view that the different tastes require distinct machinery within the cell to transduce their signals to the brain, which is responsible for processing taste perceptions.

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— **Charles S. Zuker**

The discovery also opens the way for more precise genetic manipulation of taste sensations in laboratory animals to discover how different tastes are perceived in the brain, according to Howard Hughes Medical Institute investigator Charles Zuker, who is at the University of California, San Diego.

Zuker, Nicholas Ryba of the National Institute of Dental and Craniofacial Research of the National Institutes of Health and their colleagues reported their findings in the February 7, 2003, issue of the journal *Cell*.

The research team reported that two enzymes found in the same signaling pathway in the cell were necessary for mice to process sweet, bitter and umami tastes.

According to Zuker, the effort to identify common components of the cell machinery involved in taste was driven by two goals. "One, is that we wanted to be able to manipulate the function of the various taste modalities, to understand taste processing," he said. "We might normally seek to knock out the receptors themselves, which is feasible with sweet receptors, since there are only a couple. But there are thirty bitter-taste receptors, which would be

practically impossible to eliminate.

“Our other goal was to make sense of the extraordinary complexity in the scientific understanding of the signaling pathways involved in taste reception. We believed that it didn't make sense for there to be multiple pathways, since all the taste receptors belonged to only a couple of families (of proteins).”

When the researchers screened a range of taste receptor cells for commonly expressed genes, they found two, called *TRPM5* and *PLCβ2*, to be widely expressed in taste cells. To demonstrate that the two enzymes—which were known to be part of the same signaling pathway—were necessary for taste signaling, the researchers engineered and examined knockout mice that lacked either of the two enzymes. These mice, they found in both electrophysiological and behavioral tests, lacked the ability to taste sweet, bitter and umami compounds. Also importantly, noted Zuker, the knockout mice retained the ability to respond to salty and sour tastes.

“This told us that clearly salty and sour tastes operated through independent mechanisms,” said Zuker. “But it also told us that you don't need a functioning sweet, bitter or umami system for completely normal salty and sour tastes.” In another key experiment in the series, the researchers generated mice in which they restored the *PLCβ2* gene in only bitter taste receptors in the *PLCβ2*-knockout mice. While these mice still could not taste sweet or umami, their bitter-tasting ability was restored.

“This was a particularly important experiment that sought to investigate another hypothesis in the taste receptor field—that taste receptor cells are broadly tuned to all three tastes,” said Zuker. “However, we reasoned that this didn't make sense, since we had found a complete non-overlap in the expression of these different receptors in taste cells. Furthermore, sweet and bitter play very different roles in triggering behavior. The role of sweet is to indicate a caloric food source, and bitter functions as a highly sensitive alarm sensor for dangerous chemicals. “So this experiment in selective rescue of these animals quite clearly showed that restoring one modality did not restore the others, demonstrating that taste receptor cells are not broadly tuned across all modalities,” said Zuker.

The discovery of the common signaling molecules and the ability to selectively knock out or rescue taste modalities provide an invaluable tool for the next steps in understanding taste.

“We believe these findings will help us understand how tastes are encoded in the tongue and decoded by the brain,” he said. “We are now beginning to track the connectivity pattern from tongue to brain. Ultimately, we hope to develop a method by which we can visualize brain function *in vivo* during the animal's tasting response.”