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## Homing In On a Receptor for the Fifth Taste

Humans can recognize five tastes: bitter, salty, sour, sweet and umami. Of the five, however, umami is the most difficult to describe — it's the flavor associated with monosodium glutamate (MSG). Now, researchers have identified a taste receptor that responds to amino acids, including umami, and they hope to develop a more precise description of the molecular events that allow the brain to perceive the five different tastes.

With the discovery of the new receptor, scientists have now identified taste receptors for amino acids, bitter and sweet tastes. Given that many amino acids are essential components of our diet, this work may also aid understanding of how animals, including humans, regulate nutritional intake to achieve a balanced diet. Better understanding of taste receptors may permit scientists in the food industry to formulate new products that have specific tastes.

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A research team led by Howard Hughes Medical Institute investigator Charles S. Zuker at the University of California, San Diego, and Nicholas J. P. Ryba of the National Institutes of Health reported the identification of an amino-acid taste receptor in an advanced online publication in *Nature* on February 25, 2002.

Zuker's and Ryba's groups previously collaborated in discovering sweet and bitter taste receptors. After they had identified those receptors, they set their sights on finding a taste receptor for amino acids, reasoning that one must exist because it had long been known that humans have the ability to taste umami and other amino acids. "Since amino acids are essential building blocks of biologically important molecules such as proteins, it made evolutionary sense for there to be a taste pathway that would make amino

acids attractive to consume," said Zuker.

In their search for the amino acid receptor, the scientists focused on T1R receptors, a family of proteins that are distantly related to receptors in the brain that recognize the amino acid glutamate and related chemicals. Different *T1R* genes can be expressed in cells in different combinations to yield cells that respond to a specific taste. For example, *T1R2* and *T1R3*, designated T1R2+3, combine to function as a sweet receptor.

To test various receptor possibilities, the scientists devised a human cell culture method in which combinations of T1R subunits were expressed in cells. This permitted the scientists to assess how cells bearing different combinations of *T1R* genes responded to particular amino acids.

Using the cell culture technique, Greg Nelson, a graduate student in Zuker's lab, discovered that the combination of cells bearing T1R1 and T1R3 functioned as a "broadly tuned" receptor that was stimulated by many amino acids. This "T1R1+3" receptor combination was highly selective for L-amino acids, which are found in nature. D-amino acids, which are mirror images of L-amino acids and do not occur naturally, did not activate the receptor.

The scientist also tested whether their newly identified amino acid receptor candidate behaved in a manner similar to receptors that recognize glutamate. A signature of the umami taste is that it is boosted by purine nucleotides, like IMP. In the cell cultures, IMP dramatically enhanced the response of T1R1+3 to amino acids.

The researchers next examined the effects of IMP in mice. They added the chemical to the animals' taste buds, then added amino acids, and measured the specific response of nerve fibers connected to the taste buds that expressed T1R1+3. The response of these nerves was greatly enhanced by IMP.

In a final set of experiments, Nelson and his colleagues showed that mice do not taste some artificial sweeteners such as aspartame and cyclamate that humans can taste because of sequence differences in the T1R receptors of the two species.

"This last piece of the puzzle is worthy of note," said Zuker. "Changes in the sequence of taste receptors appear to be responsible for some of the difference in tasting behavior between mice and humans."

According to Zuker, discovery of the amino acid taste receptor will have important implications for understanding the machinery of taste. "When Nick Ryba and I began this collaboration a bit over four years ago, our ultimate goal was to understand how the brain knows what you just tasted," he said. "We wanted to discover how taste receptor cells are activated and how their signals travel to the brain to produce specific taste perceptions.

"To do that, we first needed to define the different taste modalities at a cellular level, so that we could then follow their connectivity maps to the

brain. The 'Holy Grail' in this field has been the receptors, and now that we know the receptors underlying three modalities – sweet, bitter and amino acid – we can begin to work on our original goal, to map this system to understand how taste is encoded," Zuker said.