

OCTOBER 31, 2003

Researchers Define Molecular Basis of Human "Sweet Tooth" and Umami Taste

Halloween turns millions of kids into candy-loving monsters with more than ample supply of confections to satisfy their "sweet tooth." Now, Howard Hughes Medical Institute researchers have moved closer to understanding why some people cannot resist the impulses brought on by sweets.

The researchers created mice with the same sweet-tooth preferences as humans by inserting the gene that codes for a human sweet-taste receptor protein into the animals. They also inserted an entirely different receptor gene into the taste cells of mice, thereby producing animals that perceive a previously tasteless molecule as sweet.

"Our own sweet preferences are likely to be not simply an issue of cultural differences, as some have argued, but to be genetically encoded."

— Charles S. Zuker

Both of these experiments demonstrate that receptor molecules on the tongue for both the sweet and "savory" umami tastes are what triggers taste cells on the tongue and palate to transmit taste signals to the brain. Umami taste responds to amino acids such as monosodium glutamate.

The researchers said their findings open the way for tracing the circuitry for sweet and umami tastes all the way to the centers in the brain that perceive those tastes. The findings also suggest that individual variations in the "sweet tooth" response may lie in subtle genetic differences in receptor molecules that perceive sweet taste.

The findings were reported in the October 31, 2003, issue of the journal *Cell* by a research team led by Howard Hughes Medical Institute investigator Charles Zuker at the University of California, San Diego, and Nicholas Ryba of the National Institute of Dental and Craniofacial Research.

"In our previous work, we reported that we had found the best candidate sweet and umami receptor molecules," said Zuker. "But there remained two

major outstanding questions. First, do these receptors function *in vivo* as taste detectors? And second, are they members of a larger group of such receptors, or are they *the receptors* for sweet and umami taste? These experiments have conclusively answered both questions; sweet and umami taste are mediated entirely by these receptors.”

The candidate receptors that Zuker, Ryba and their colleagues identified are complex proteins on the surfaces of taste cells. When stimulated, these proteins switch on internal cellular machinery, which begins the process of sending a signal about the taste to the brain. The umami receptor is a combination of two protein subunits called T1R1 and T1R3. Sweet, on the other hand, is mediated by two different receptors: a combination of T1R2 and T1R3, which responds to natural and artificial sweeteners, and T1R3 which responds only to high concentrations of sugars.

In their experiments, Grace Zhao and colleagues first produced knockout mice lacking each one of the three types of subunits. To test the response of the knockout mice to sweet or umami tastes, they measured the behavioral preference of the mice for either plain or flavored water. They also measured the direct response of the taste cells to sweet- or umami-tasting chemicals by performing physiological studies on the nerves that carry taste information.

Their studies showed that mice lacking either the T1R1 or T1R3 subunits lost all response to umami tastes. And knockout mice lacking either T1R2 or T1R3 lost preference for almost all sweet tastes. However, those mice retained some ability to respond to high concentrations of natural sugars, suggesting that either of the subunits could function on its own as a “low-affinity” sweet receptor. When the scientists produced double-knockout mice lacking both components of the sweet receptors, those animals lost all response to sweet-tasting chemicals.

Additional cell-based studies revealed that the T1R3 protein alone responds to high concentrations of natural sugars, but not to lower concentrations, or to artificial sweeteners. “This finding may explain why artificial sweeteners never attain the level of sweetness that natural sugars do,” said Zuker. “Artificial sweeteners activate only the T1R2+T1R3 combination of subunits in the sweet receptor, while natural sugars also activate T1R3 alone.”

One puzzle about sweet taste is why humans can taste a number of natural and artificial sweeteners that rodents cannot. These include the intensely sweet (to humans) proteins monellin and thaumatin found in certain fruits, and the artificial sweetener aspartame.

To demonstrate that the human “sweet-tooth” preferences lie in the receptors, the researchers generated mice with the human T1R2 receptor, which is significantly different in sequence from the mouse counterpart. “We found that these mice with the human receptors like the same sweet molecules that we humans do,” said Zuker. “They loved both the sweet proteins and the aspartame flavor.

“This proves that the species differences are a reflection of the sequence of the receptors, and strongly suggests that our own sweet preferences are likely to be not simply an issue of cultural differences, as some have argued, but to be genetically encoded.” For example, slight genetic differences in receptor proteins “might explain why one person needs five spoons of sugar in his coffee and another needs only two—because the first person's sweet receptors need more sugar to get the same kick.”

To demonstrate conclusively that the responses of the taste cells themselves are what determine taste perception, Zhao and her colleagues performed an even more radical genetic replacement. They introduced into the sweet-tasting cells of mice a receptor for an entirely unrelated, synthetic opioid compound.

When the mice were presented with the compound, “much to our delight, these mice were strongly attracted to this novel chemical,” said Zuker. “They thought it was sweet, even though we humans (or even the very same mice prior to expressing the gene) would find it tasteless.”

The ability to genetically manipulate taste cells in such a way gives researchers a major entrée into the taste centers of the brain. “Now we can follow the connectivity from the tongue all the way to the brain and begin to define what cells in the brain are responsible for behavioral responses to each of these taste modalities,” he said. By inserting foreign receptors into taste cells, said Zuker, researchers can be assured that they are tracking the behavior of just that taste circuit and not others that might be triggered by the same receptor—in essence “a labeled line.”