HHMI
HOWARD HUGHES MEDICAL INSTITUTE

RESEARCH NEWS

MARCH 10, 2005

Researchers Discover How Bitter Taste is Perceived

For the first time, researchers have discovered precisely how animals detect bitter tastes and how they might manage to avoid toxic and noxious substances. Their studies show that specific cells of the tongue govern detection of bitter substances.

In a particularly intriguing experiment, the researchers engineered mice to perceive bitter-tasting chemicals as sweet, and the animals relished the taste of those noxious compounds as if they were sugar. The same studies also demonstrated that taste cells are “hard-wired” to signal the presence of a particular taste to the brain, regardless of what taste receptors they possess.

This work, along with the group's recent discoveries on the biology of sweet and umami taste, opens a research pathway to tracing taste processing into higher brain regions where animals and humans make complex judgments about tastes - like going from the subtle “off taste” of spoiling milk to the complex, unique flavor of fois gras.

"We know we can mask a bitter taste by adding more sweet-tasting compounds. We want to find out where in the brain is this comparator that integrates the input from the taste system and decides, Do I like this taste or dislike it?"
- Charles S. Zuker

The researchers published their findings in the March 10, 2005, issue of the journal *Nature*. They were led by Howard Hughes Medical Institute investigator Charles Zuker at the University of California at San Diego and Nicholas Ryba of the National Institute of Dental and Craniofacial Research at the National Institutes of Health.

A key question spurring the research, said Zuker, was the role of a family of protein receptors called T2R, which were suspected to function as receptors for bitter-tasting substances in the taste cells of the tongue. Previous biochemical and genetic studies by Zuker's group had indicated their role in bitter taste, but it had not been firmly established.

“There were two major outstanding controversies,” said Zuker. “One was whether these three dozen or so T2R receptors were the principal receptors for bitter tastants, and whether individual “bitter sensing cells” are tuned to detecting small subsets of bitter tastants, or function as universal detectors for all bitter tastes. The other controversy was whether different taste qualities, like sweet and bitter, are encoded by the activation of distinct cell types and connectivity pathways (labeled lines), or as many taste researchers had previously suggested, by receptor cells tuned to multiple taste qualities”

To discover whether T2R receptors were both necessary and sufficient to detect bitter tastes, the researchers engineered mice to have altered or absent T2R receptors in their taste cells and tested the animals' response to bitter substances. The researchers found that mice given only human T2R receptors now displayed dramatic aversion to a bitter chemical to which humans, but not mice, were normally sensitive.

In other experiments, the researchers knocked out in mice a T2R receptor that was sensitive only to the compound cyclohexamide—normally highly noxious to mice and humans. They found that these mice lost sensitivity and aversion to the chemical in behavioral taste tests, and readily drank water containing the chemical.

“These experiments showed that T2R receptors are both necessary and sufficient for bitter taste sensation,” said Zuker. “Importantly, the fact that we can `humanize' the taste response of these mice by giving them human receptors also illustrates how the evolutionary tuning of receptors may account for the differences in taste sensitivity among species.”

The researchers also demonstrated that bitter-sensing cells are not specialized for specific bitter tastes, but are broadly tuned to respond to most, and perhaps all bitter tastes. When they engineered mice to lack all taste reception, and then selectively restored function only in cells that express T2R receptors, they found that those mice now had a fully functional bitter taste system.

In the most dramatic experiment, the researchers proved that taste cells are functionally segregated and that it is the wiring of the taste cells themselves to higher brain regions, and not their receptors, which governs taste perception. The researchers expressed a receptor for a bitter-tasting compound in taste cells that normally detect sweet tastes. They found that these mice drank water laced with the bitter chemical with relish, as if it were sweet.

“There has long been an argument that the way taste is encoded at the tongue is by having cells that are broadly tuned across multiple taste qualities - for example cells that detect both sweet and bitter, or bitter and umami, etc.” said Zuker. “And the argument was that the brain decodes the pattern of activity across these cells to figure out whether you've tasted something bitter, sweet, or some combination. This never made sense to us, because why would you want to encode modalities that represent such extraordinarily divergent behaviors like attraction (sweet) and aversion (bitter) using the very same receptor cells, in other words why would you want to encode signals that meant life and death in the cells?

“Instead, we argued that taste information should be conveyed through `labeled lines,' with taste receptor cells individually tuned to distinct modalities. Indeed, that is precisely what we have proven with these experiments. Furthermore, a fundamental outcome of these studies is the demonstration that the “taste” of a compound has nothing to do with the quality of the compound; it is simply a reflection of the type of taste cell being activated.”

According to Zuker, establishing the details of the taste machinery will enable researchers to tackle the question of how the brain sorts out complex tastes. “Somewhere up the neural processing pathway there is an integration of taste information, in which the animal compares various taste modalities and decides what its response should be,” he said. “For example, we know we can mask a bitter taste by adding more sweet-tasting compounds. We want to find out where in the brain is this comparator that integrates the input from the taste system and decides, `Do I like this taste or dislike it?' We ultimately want to know how the brain integrates the various inputs from the taste system—bitter, sweet, umami, salt and sour—and uses that information to trigger selective behavioral and physiological responses,” he said.