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Search for Taste Receptors Yields Sweet Success

Using biochemical clues as a guide to scout massive databases of genetic sequences, Howard Hughes Medical Institute (HHMI) researchers at Harvard Medical School have identified a family of candidate genes in humans and mice that code for receptors that sense bitter-tasting chemicals.

According to the researchers, the discovery opens the way for the identification of additional receptors that detect bitter and sweet tastes. The finding also gives researchers new probes with which to trace the wiring of the taste perception pathways into the brain itself.

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— **Linda B. Buck**

Linda Buck, an HHMI investigator at Harvard Medical School, and her colleagues Hiroaki Matsunami and Jean-Pierre Montmayeur published their findings in the April 6, 2000, issue of *Nature*.

Buck's group's discovery of bitter taste receptor genes complements recently published findings of the same gene family by another research team led by HHMI investigator Charles Zuker at the University of California, San Diego. Zuker's team published its findings in the March 17, 2000, issue of the journal *Cell*.

Receptors are proteins that nestle in the cell's surface and bind specific chemicals in much the same way that a key fits into a lock. When activated by a chemical, receptors trigger molecular signals within a cell that alter the cell's metabolism. In the case of taste receptors, chemicals impinging on the taste buds trigger nerve impulses that travel to the brain, where taste information is processed.

Buck and her colleagues began their search by drawing on previous discoveries by other scientists studying taste, including Robert Margolskee, an HHMI investigator at Mount Sinai School of Medicine. Margolskee had obtained evidence that receptors for both bitter and sweet chemicals were coupled to a common signaling molecule inside the cell a G-protein that he called gustducin. In launching the search for the genes that expressed such taste-related G-protein coupled receptors (GPCRs), Buck and her colleagues theorized that such receptors would be distantly related to other receptors in the body that signal using other G-proteins.

"In the sense of smell, we previously found one thousand different-but-related odor receptors," said Buck. "Interestingly, these receptors all couple to the same molecules inside the cell to transmit a signal. We suspected that the same would be true for taste."

Buck and her colleagues narrowed their search for taste-related GPCRs to a region of a mouse chromosome that other scientists had found to be involved in the ability to taste a particular bitter substance. Using the Jackson Laboratory Mouse Genome Informatics website, Buck's team pinpointed the promising taste-related region of DNA, called SOA, in the mouse genome and determined that the corresponding region in humans was in a specific location on human chromosome 12. Using the Human Genome Sequence (HGS) database at the National Center for Biotechnology Information, they then scanned that region of chromosome 12 for genes that specify novel receptors distantly related to known GPCRs.

To do this, the scientists used another database containing gene sequence data for known GPCRs. They compared a range of GPCR genes with the DNA sequences available for chromosome 12 in an attempt to detect any similarities. The computer analysis revealed a slight similarity between a particular GPCR gene for a chemical receptor and a chromosome 12 gene in the focus region. Using the chromosome 12 gene for further scans, they uncovered a cluster of related but distinct genes in the same chromosomal region.

"It was like magic," said Buck. "All of a sudden all of these receptor genes showed up that were related, and there was a whole cluster on chromosome 12." Further exploration of the HGS database also revealed related GPCRs on regions of chromosomes 7 and 5 the latter of which contains a region of DNA that governs a person's ability to taste a particular bitter chemical.

"We are certain that these receptors are just the tip of the iceberg," said Buck, indicating that more taste receptor genes are sure to surface as the Human Genome Project is completed. "Odorant receptors are known to be scattered throughout the human genome, and we believe the same will be true for taste receptors. We predict that there are probably 50 to 100 of these receptors."

Discovering the candidate taste receptors likely represents only the beginning of a long exploration of the sense of taste, said Buck.

"These findings open the way for a molecular understanding of taste," she said. "For example, we don't know how taste receptors can recognize so many different chemicals with diverse structures, and yet perceive them all as having the same taste, whether bitter or sweet.

"Also, with these receptors, we now have the tools to trace neuronal signals for a particular taste all the way from the taste buds through many connections into the brain. And then we hope to see where the information from the receptor is actually targeted and how it is organized in the brain, and ultimately to learn something about the perception of different tastes."

Among the many possible practical benefits, said Buck, might be the development of chemicals that block the bitter taste of medicines, which would considerably increase the likelihood that patients would maintain their drug regimens.