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Researchers Discover How Mammals Distinguish Different Odors

Smell is perhaps the most exquisitely sensitive and complex of all the senses, and it has also been the most perplexing for scientists to decipher. Researchers have wondered, for example, how small amounts of a particular chemical can smell enticing, while large amounts of the same chemical are overpowering. Now, researchers from the Howard Hughes Medical Institute (HHMI) at Harvard Medical School and colleagues from Japan have solved one of olfactory research's biggest puzzles: How can the nose with a relatively small number of olfactory receptors have the sensitivity to discriminate roughly 10,000 different odors?

HHMI investigator Linda Buck and HHMI associate Bettina Malnic at Harvard Medical School, and colleagues Junzo Hirono and Takaaki Sato at the Life Electronics Research Center in Amagasaki, Japan, appear to have solved this puzzle with one stunning finding. In the March 5, 1999, issue of the journal *Cell*, they report that the sense of smell in mammals is based on a combinatorial approach to recognizing and processing odors. Instead of dedicating an individual odor receptor to a specific odor, the olfactory system uses an "alphabet" of receptors to create a specific smell response within the neurons of the brain.

"Each receptor is used over and over again to define an odor, just like letters are used over and over again to define different words," said Buck. As in language, the olfactory system appears to use combinations of receptors (words) to greatly reduce the number of actual receptor types (letters) required to convey a broad range of odors (vocabulary).

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Nature is not unaccustomed to using combinatorial code: The four "letters" in the genetic code A, C, G and T (abbreviations for the nucleotides adenine, cytosine, guanine and thymine) allow the creation of a nearly infinite number of genetic sequences. The findings of Buck and her colleagues are, however, the first confirmation that the nerves that constitute the mammalian olfactory system also use a combinatorial approach.

As odors enter the nose and negotiate a hairpin-like turn at the top of the nasal cavity, they encounter the olfactory epithelium, a patch of cells on the wall of the nasal cavity. The olfactory epithelium contains about five million olfactory neurons. Buck and her colleagues had previously discovered that each olfactory neuron expresses only one of roughly 1,000 types of olfactory receptors on its surface.

When an odor excites a neuron, the signal travels along the nerve cell's axon and is transferred to the neurons in the olfactory bulb. This structure, located in the very front of the brain, is the clearinghouse for the sense of smell. From the olfactory bulb, odor signals are relayed to both the brain's higher cortex, which handles conscious thought processes, and to the limbic system, which generates emotional feelings.

"This is probably why an odor can evoke powerful emotional responses as well as convey factual information," Buck explained. "But this also leads to an interesting question: Where exactly does information about different odors end up? It may be that signals generated by some receptors for example, those that recognize rotting food can elicit an innate rather than a learned response."

Buck's group has also uncovered other clues about the sense of smell. In 1994, they reported in *Cell* that neurons expressing the same kind of odor receptor were scattered throughout the olfactory epithelium, but their axons all converged at very specific points in the olfactory bulb. The dispersion within the epithelium, says Buck, can help protect the sense of smell should a portion of the epithelium become damaged by infection. And at the other end, convergence of signals from thousands of neurons with the same receptor may increase sensitivity to low concentrations of odors.

In their current study, the investigators exposed individual mouse neurons to a range of odorants. Using a technique called calcium imaging, the researchers detected which nerve cells were stimulated by a particular odor. When an odorant molecule binds to its odor receptor, calcium channels in the membranes of the nerves open and calcium ions pour inside. This generates an electrical charge that travels down the axon as a nerve signal. Calcium imaging measures this influx of calcium ions.

"Using this method we were able to show three things," said Buck. "First, a single receptor can recognize multiple odorants. Second, a single odorant is

typically recognized by multiple receptors. And third, we also found that different odorants are recognized by different combinations of receptors. This indicates that the olfactory system uses a combinatorial coding scheme to encode, or represent, the identities of odors.

"In other words, different combinations explain how 1,000 receptors can describe many thousands of odors," she added.

In one set of experiments, for example, Buck and her colleagues demonstrated that even slight changes in chemical structure activate different combinations of receptors. Thus, octanol smells like oranges, but the similar compound octanoic acid smells like sweat.

Similarly, the investigators found that large amounts of a chemical bind to a wider variety of receptors than do small amounts of the same chemical. This would explain why a large whiff of the chemical indole smells putrid, while a trace of the same chemical smells flowery.

"It's just a matter of the alphabet," said Buck.