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RESEARCH NEWS

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Richard Axel and Linda Buck Awarded 2004 Nobel Prize in Physiology or Medicine

The Nobel Assembly at the Karolinska Institute announced this morning that the 2004 Nobel Prize in Physiology or Medicine was awarded to Richard Axel, an HHMI investigator at Columbia University College of Physicians and Surgeons, and Linda Buck, an HHMI investigator at the Fred Hutchinson Cancer Research Center. The scientists were honored for their discoveries that clarify how the olfactory system works.

Axel and Buck discovered a large gene family, comprised of some 1,000 different genes (three per cent of human genes) that give rise to an equivalent number of olfactory receptor types. These receptors are located on the olfactory receptor cells, which occupy a small area in the upper part of the nasal epithelium and detect the inhaled odorant molecules.

In 1991 Axel and Buck—who was then a postdoctoral fellow in Axel's lab—discovered a family of genes that encode the odorant receptors of the olfactory epithelium, a patch of cells on the wall of the nasal cavity. The olfactory epithelium contains some 5 million olfactory neurons that send messages directly to the olfactory bulb of the brain. 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.

"I had tried so many things and had been working so hard for years, with nothing to show for it. So when I finally found the genes in 1991, I couldn't believe it! None of them had ever been seen before. They were all different but all related to each other. That was very satisfying."

- Linda B. Buck

Each olfactory neuron in the epithelium is topped by at least 10 hair-like cilia that protrude into a thin bath of mucus at the cell surface. Somewhere on these cilia, scientists were convinced, there must be receptor proteins that recognize and bind odorant molecules, thereby stimulating the cell to send signals to the brain.

The receptor proteins would be the key to answering two basic questions about olfaction, explained Axel. First, how does the system respond to the thousands of molecules of different shapes and sizes that we call odorants—"does it use a restricted number of promiscuous receptors, or a large number of relatively specific receptors?" And second, how does the brain make use of these responses to discriminate between odors?

The string of discoveries that totally changed the study of olfaction resulted from a new emphasis on genetics. Instead of hunting for the receptor proteins directly, Axel and Buck looked for genes that contained instructions for proteins found only in the olfactory epithelium.

Their efforts produced nothing at first. "Now we know why our initial schemes failed," said Axel. "It's because there are a large number of odorant receptors, and each was expressed only at a very low level."

Finally, Buck came up with what Axel calls "an extremely clever twist." She made three assumptions that drastically narrowed the field, allowing her to zero in on a group of genes that appear to code for the odorant receptor proteins.

Her first assumption—based on bits of evidence from various labs—was that the odorant receptors look a lot like rhodopsin, the receptor protein in rod cells of the eye. Rhodopsin and at least 40 other receptor proteins criss-cross the cell surface seven times, which gives them a characteristic, snake-like shape. They also function in similar ways, by interacting with G proteins to transmit signals to the cell's interior. Since many receptors of this type share certain DNA sequences, Buck designed probes that would recognize these sequences in a pool of rat DNA.

Next, she assumed that the odorant receptors are members of a large family of related proteins. So she looked for groups of genes that had certain similarities. Third, the genes had to be expressed only in a rat's olfactory epithelium.

"Had we employed only one of these criteria, we would have had to sort through thousands more genes," said Axel. "This saved several years of drudgery."

Buck recalls that "I had tried so many things and had been working so hard for years, with nothing to show for it. So when I finally found the genes in 1991, I couldn't believe it! None of them had ever been seen before. They were all different but all related to each other. That was very satisfying."

The discovery made it possible to study the sense of smell with the techniques of modern molecular and cell biology and to explore how the brain discriminates among odors.

It also allowed researchers to "pull out" the genes for similar receptor proteins in other species by searching through libraries of DNA from these species. Odorant receptors of humans, mice, catfish, dogs, and salamanders have been identified in this way.

The team's most surprising finding was that there are so many olfactory receptors. The 100 different genes the researchers identified first were just the tip of the iceberg. It now appears that there are between 500 and 1,000 separate receptor proteins on rat and mouse—and probably human—olfactory neurons.