Discovering the Secret of Smell

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Humans and animals perceive and interact with the world through five main senses – vision, hearing, touch, taste and smell. How do our senses work? What enables us to watch a movie, listen to music, feel the texture of fine fabrics, and enjoy the bitterness of beer or the stimulating aroma of freshly brewed coffee? Scientists have been asking these questions for over 100 years, and great strides have been made in understanding mechanisms of the visual and auditory senses. We learned how photoreceptor cells in the eye respond to light, and how hair cells in the ear respond to sound. In taste and smell, the pace of research was slower because it was hard to determine exactly how cells of the tongue or nose respond to different chemicals.

Two major breakthroughs in understanding olfaction ¬– the sense of smell – were made about 20 years ago. First, it was discovered that when odors are sniffed, sensory neurons in the nose produce a specific signal, cyclic AMP, that enables them to relay odor information to the brain1,2. A second big breakthrough came in 1991, when Linda Buck and Richard Axel identified a large family of genes coding for olfactory receptors, specialized proteins that detect and recognize odor molecules3. The size of this family was remarkable, with over 350 different receptors in the human nose, and over 1,000 in the mouse nose. This great diversity of receptors gives us the ability to smell a vast number of chemicals as distinct odors. However, the brain faces a serious challenge in managing the enormous amounts of odor information collected by hundreds or thousands of different receptors. How is this information processed so that we can perceive the world of scents?

An early clue to the puzzle came from the work of the famous neuro-anatomist Santiago Ramón y Cajal, who applied the silver staining method of Golgi to highlight the structure of the olfactory bulb, the first part of the brain receiving odor information from the nose4. The bulb was found to contain numerous ball-shaped structures, the glomeruli, which were later hypothesized to be basic units of odor coding5. This was confirmed decades later when olfactory receptors were identified, and a gene-labeling technique revealed that sensory neurons in the nose with distinct olfactory receptors send their nerve fibers to distinct glomeruli6. Therefore, when inhaled odors are captured by olfactory receptors their molecular structures are profiled and mapped to precise patterns of glomeruli uniquely identifying their chemical makeup6.

In my laboratory, we study basic questions about receptors and glomeruli that code for familiar odors, such as the smell of delicious food or the fragrance of flowers. Which receptors in the nose detect odors with different chemical properties? How do glomerular patterns change when several odors are blended into complex mixtures?8 Are odors that access the nose directly from the mouth coded differently for food flavors?9 We are investigating how the brain analyzes and selects glomerular patterns for odor recognition and perception. For example, we discovered that neurons in glomeruli transmit precisely timed signals that may be important for odor coding10. Recently, we found that two cellular modulators, nitric oxide (NO)11-12 and cholecystokinin (CCK)13, can influence olfactory bulb neurons conveying odor signals to higher brain centers. This could sensitize glomeruli to certain odors, which may help focus our attention on significant smells in the environment, or improve our odor memories.

Research into neural mechanisms of olfaction is motivated not just by pure curiosity, but also by the potential for applications. In medicine, research on olfaction could help our understanding of neurological disorders such as epilepsy, Parkinsons Disease and Alzheimers Disease. Other spin-offs might include advances in electronic olfaction, or "e-noses", where new engineering could be inspired by seeing how living olfactory systems detect and discriminate odors. Deciphering odor codes of complex mixtures and flavors could spur new products in food and beverage industries. However, the greatest impacts may arise from novel insights that we cannot imagine, and that can only be revealed by expanding the frontiers of human knowledge.

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