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Opening the Window to Odor Space

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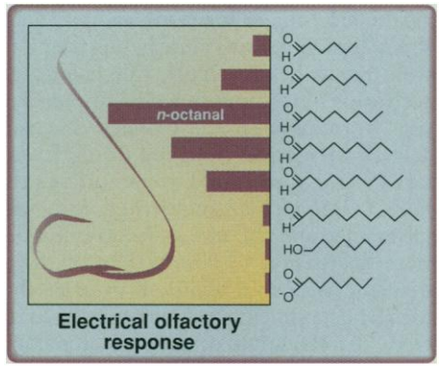
Ask someone to describe a sound and you will immediately learn about the loudness and the pitch. A similar query about a visual scene will produce descriptions of the brightness and the color. These simple characterizations of the intensity and frequency of sensory stimuli allow easy understanding of how the brain codes auditory and visual information.

The qualities of an odor stimulus are much more difficult to place on linear spectra. Psychophysical experiments suggest that in the olfactory world of the brain, there exists a multidimensional odor "space" that characterizes odorant stimuli. And in spite of considerable progress in elucidating the molecular basis of olfactory signal transduction, there has been little progress in linking putative odorant receptor proteins with their cognate ligands. A report in this issue on page 237 (*1*) begins to shed light on the specificity of individual olfactory receptors and demonstrates their ability to mediate the detection of odorant stimuli in vivo, paving the way for a clearer definition of odor space.

In 1991, Buck and Axel (*2*) discovered a large gene family that encodes serpentine receptors preferentially expressed in subpopulations of olfactory neurons, fulfilling earlier hypotheses regarding odor discrimination. If each cell expresses a single receptor type, as now seems likely, then the signal propagated to the brain by the receptor cells may reflect the intrinsic ligand specificity of the unique receptor expressed in that cell. Unfortunately, it has not been possible to reproduce in expression systems the robust activation of odorant receptors with single ligands. The inefficient translocation of expressed receptors to the plasma membrane may partially explain these failures. Membrane preparations from insect cells infected with receptor-expressing recombinant virus have produced only modest and relatively nonspecific second messenger responses (*3*).

Zhao *et al.* have now taken an elegant approach to demonstrate receptor function and specificity. Recombinant adenovirus expressing a hybrid mRNA encoding the I7 odorant receptor and green fluorescent protein (GFP) were introduced into the nasal cavity of rats. Imaging of the GFP in the olfactory neuroepithelium revealed that up to 10% of the cells expressed GFP and that the virus selectively infected the neuronal cell population. The authors assessed the electrophysiological response of wild-type and infected epithelium to individual odorant application by a measurement of transient, induced electrical potential, the electro-olfactogram. Among the more than 50 odorants initially tested, only a single compound,



The knowing nose. One olfactory receptor responds to *n*-octanal.

n-octanal, produced elevated responses in recordings from the I7 recombinant adenovirus-infected tissue. Smaller responses were observed for the structurally related straight-chain aldehydes, which contain one fewer and up to two additional methylene groups. Octanoic acid and octanol, which are similar to *n*-octanal, unexpectedly failed to produce a specific response in the I7 receptor–expressing tissue. As a further confirmation of the ability of the I7 receptor to transduce an octanal signal, dissociated GFP (and presumably I7 receptor)-expressing cells were examined by whole-cell patch electrophysiology. Each of the cells produced a characteristic depolarization in response to the ligand, *n*-octanal.

The use of real olfactory neurons to direct the expression of introduced receptors appears to circumvent the previous difficulties in protein translocation and receptor function. But the disadvantage is that additional factors expressed by the sensory neurons or the surrounding cells in the tissue could still contribute to ligand binding in this in vivo system. For example, odorant binding proteins may help to present odorants to the receptor (*4*).

These studies by Zhao *et al.* with mammalian receptors follows closely on the heels of functional characterization of chemoreceptors from *Caenorhabditis elegans* (*5*). The availability of defined ligands and cognate receptor proteins in two different systems now provides valuable tools to establish an in vitro expression system more amenable to direct determination of affinity and structural specificity.

The similarities and differences between the mammalian olfactory system and the *C. elegans* chemosensory system are readily apparent. Although the receptor families in the two organisms comprise more than 100 members, they share essentially no primary sequence homology (*6*). The rat I7 receptor as well as the *odr-10* receptor of *C. elegans* (responsible for diacetyl detection) (*7*) display high ligand selectivity (*8*). But the two organisms differ significantly in the way these signal are used. For the worm, the entire repertoire of receptors is expressed in only a handful of cells, perhaps reflecting it's need to determine only the attractive or repulsive nature of chemosensory stimuli. In mammals, where identity of the stimulus is more important, an elaborate system of cellular selectivity and axonal convergence has evolved. More examples of receptor specificity in the mammalian system will be needed before we know whether odorant coding is achieved uniquely through highly specific receptors or by the combined processing of signals from narrowly "tuned" and broadly tuned classes of receptors.

The mammalian olfactory system is one of the best models to examine structure-function relations between ligands and their receptors. The large family of related proteins that may couple to a common intracellular second messenger system, combined with the fragrance chemists' almost limitless collection of compounds, is a rich vein for future mining. The pharmacologist and the sensory psychophysicist may finally be able to join forces and decipher the code with which the brain determines the identity of simple and complex odorant stimuli.

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References

1. H. Zhao *et al.*, *Science* **279**, 237 (1998).
2. L. Buck and R. Axel, *Cell* **65**, 175 (1991).
3. K. Raming *et al.*, *Nature* **361**, 353 (1993).
4. J. Pevsner, R. R. Reed, P. G. Feinstein, S. H. Snyder, *Science* **241**, 336 (1988).
5. Y. Zhang, J. Chou, J. Bradley, C. Bargmann, K. Zinn, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 12162 (1997).
6. E. R. Troemel, J. H. Chou, N. D. Dwyer, H. A. Colbert, C. I. Bargmann, *Cell* **83**, 207 (1995).
7. P. Sengupta, J. H. Chou, C. I. Bargmann, *ibid.* **84**, 899 (1996).
8. P. Sengupta, H. A. Colbert, C. I. Bargmann, *ibid.* **79**, 971 (1994).