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The Molecular Architecture of Odor and Pheromone Sensing in Mammals

Review

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Olfaction is an ancient sense. Its precursors can be found in the most primitive single-celled organisms, reflecting the need of every organism to sense its chemical milieu. In mammals, the olfactory system can detect and distinguish a vast number of volatile chemicals with a large variety of structures (Beets, 1970; Shepherd, 1988). It seems to have evolved to sense almost any volatile chemical it might encounter. However, the olfactory system is also responsible for the sensing of pheromones, chemicals released by animals that act on conspecifics to regulate populations of animals and their social interactions (Wilson, 1963; Shepherd, 1988). Pheromones elicit programmed neuroendocrine changes and innate behaviors, suggesting a need for a very precise recognition process.

How does the olfactory system meet these dual requirements for general odor sensing and the generation of stereotyped responses to specific pheromones? Studies in both insects and mammals suggest that it does it by segregating odor and pheromone detection in different sensory neurons and in different neural pathways in the brain (Halpern, 1987; Wysocki and Meredith, 1987; Hildebrand and Shepherd, 1997). Structural and functional studies of these pathways have provided insight into many aspects of odor and pheromone sensing (Halpern, 1987; Kauer, 1987; Wysocki and Meredith, 1987; Shepherd, 1988; Buck, 1996; Hildebrand and Shepherd, 1997; Mori et al., 1999). In recent years, the discovery of multigene families encoding olfactory receptors has provided molecular tools with which to further explore these processes in both vertebrates and invertebrates (Buck and Axel, 1991; Ngai et al., 1993; Troemel et al., 1995; Sengupta et al., 1996; Clyne et al., 1999; Vosshall et al., 1999). This review will focus on what these molecular studies have revealed about the mechanisms underlying odor and pheromone sensing in mammals.

Odorants and Pheromones

Mammals can distinguish an enormous diversity of odorants that vary in size, shape, functional groups, and charge (Beets, 1970). In contrast, only a few mammalian pheromones have been identified, though many different pheromone effects that can be elicited by urine or other bodily secretions have been described (Halpern, 1987; Wysocki and Meredith, 1987; Novotny et al., 1990; Keverne, 1999). In rodents, these include stereotyped male and female mating behaviors, aggressive behaviors by males or lactating females toward intruder males, inhibition of estrous cycling and puberty delay in group-housed females, reversal of these female-induced effects by males, and pregnancy termination caused by exposure of a female to a male that is genetically different from the inseminating male (the Bruce Effect). In the Bruce Effect, it appears that a pheromone effect can be coupled with the detection of "individuality cues" that result from genetic variation within a species, including differences at major histocompatibility loci.

Odor and Pheromone Circuits

In mammals, odorants are detected in the olfactory epithelium (OE) that lines the nasal cavity (Shepherd, 1988) (Figure 1). Signals generated in olfactory sensory neurons in the OE in response to odorants are relayed through the main olfactory bulb (MOB) to the olfactory cortex (OC) and then to other brain areas. Via these pathways, odor signals ultimately reach higher cortical areas involved in the conscious perception of odors, as well as limbic areas, such as the amygdala and hypothalamus, that are involved in emotional and motivational responses.

Most mammals have a second olfactory sense organ, called the vomeronasal organ (VNO) (Figure 1). The VNO is a tubular structure in the nasal septum that is connected to the nasal cavity by a small duct. Removal of the VNO, or severing its connection to the brain, interferes with pheromone effects but not with general odor sensing. Although some pheromones are sensed in the OE (Dorries et al., 1997), these observations have suggested that the VNO may be specialized to detect pheromones (Halpern, 1987; Wysocki and Meredith, 1987; Keverne, 1999). Sensory neurons in the VNO are connected to the accessory olfactory bulb (AOB). From there, signals are transmitted to areas of the amygdala and hypothalamus that have been implicated in certain pheromone effects and are, for the most part, different from those that receive odor signals.

Receptors for Odorants and Pheromones

The initial detection of olfactory stimuli is mediated by three distinct families of olfactory receptors, each encoded by a multigene family (Figure 2). One family of ~1000 genes codes for odorant receptors (ORs) in the OE (Buck and Axel, 1991). Comprising approximately 1% of the genomic complement of genes, this family is by far the largest identified in the genome of any species. ORs are members of the 7 transmembrane domain, G protein-coupled receptor (GPCR) superfamily. They are extremely diverse in amino acid sequence, consistent with an ability to recognize a wide variety of structurally diverse odorants (Buck and Axel, 1991; Levy et al., 1991; Lancet and Ben-Arie, 1993; Ngai et al., 1993; Mombaerts, 1999).

The other two olfactory receptor families are expressed in the VNO: the V1R family, with about 35 members (Dulac and Axel, 1995), and the V2R family, with about 150 members (Herrada and Dulac, 1997; Matsunami and Buck, 1997; Ryba and Tirindelli, 1997). So

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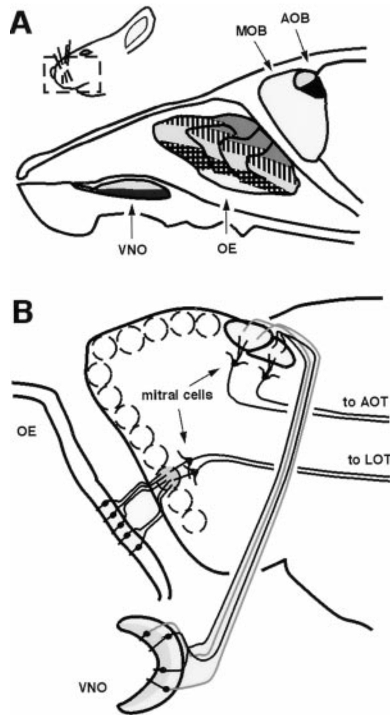


Figure 1. The Neural Circuitry of Odor and Pheromone Sensing: the Sensory Epithelia and the Olfactory Bulb

(A) Locations of the OE, VNO, MOB, and AOB.

(B) Axonal projections from the OE and VNO to the MOB and AOB, respectively. AOT, accessory olfactory tract. LOT, lateral olfactory tract.

far, no ligands for V1Rs or V2Rs have been identified. However, given their expression in the VNO, they are considered to be candidate receptors for pheromones. Like ORs, V1Rs and V2Rs are members of the GPCR superfamily, and members of both VR families are diverse, suggesting that different family members may recognize different ligands.

V2Rs differ from ORs and V1Rs in having a very large N-terminal extracellular domain. The V2Rs are related to metabotropic glutamate receptors, whose large N-terminal domains bind ligand (Okamoto et al., 1996). In contrast, in many GPCRs with short N termini like ORs and V1Rs, ligand appears to bind in a pocket that is formed in the membrane by a combination of the transmembrane domains (Strader et al., 1995). Consistent with a similar mode of ligand binding in ORs, a single amino acid change in one transmembrane domain of an OR has been shown to alter its odorant specificity (Krautwurst et al., 1998).

Curiously, many V2R cDNAs lack segments that encode bits of the N terminal domain, resulting in truncated proteins that have no transmembrane domains. The missing segments appear to correspond to individual exons (Matsunami and Buck, 1997). However, it is not known whether variant mRNAs are generated from potentially functional genes by alternative RNA splicing or from pseudogenes in which one or more exons is aberrant or absent.

Why do the VNO and OE use different sensory receptors? One possibility is that the different receptor families are uniquely suited to the distinct functions they presumably subserve: the perceptual discrimination of a multitude of volatile chemicals versus the generation of programmed endocrine and behavioral responses to pheromones. Recent studies indicate that individual ORs can recognize multiple odorants (see below). V1Rs and V2Rs might, instead, be selective for specific pheromones, thereby preventing inadvertent behavioral or physiological responses to inappropriate stimuli, such as odorants, or pheromones of a different species.

Another question is why the VNO employs two distinct families of receptors to detect sensory ligands. Although the different structures of V1Rs versus V2Rs suggest that they might recognize different types of chemicals, ligands for these receptors have not yet been identified, and the respective functions of the two receptor families are unknown. It has been speculated that having a remote ligand-binding site in the N-terminal domain might allow V2Rs to rapidly evolve to accommodate the recognition of new pheromones that arise during the formation of new species, thereby aiding in speciation (Matsunami and Buck, 1997). The abundance of aberrant V2R mRNAs might also reflect such a process.

Interestingly, fish, which do not have VNOs, do have V2R-like receptors, but they are expressed along with ORs in the fish OE (Cao et al., 1998; Naito et al., 1998; Speca et al., 1999). Electrophysiological recordings indicate that the fish OE detects amino acids and bile acids as well as pheromones (Sorenson and Caprio, 1998).

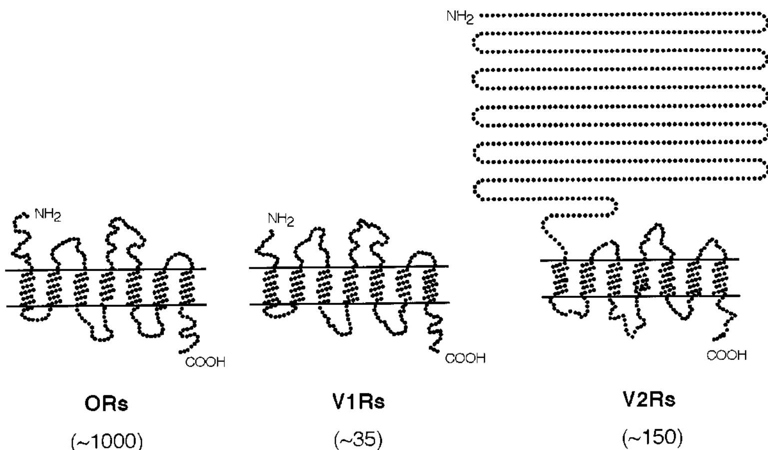


Figure 2. Receptors for Odorants and Pheromones

One fish V2R was recently found to recognize arginine (a fish odorant), suggesting that other fish V2Rs may also detect amino acids (Speca et al., 1999). It remains to be seen whether some fish V2Rs recognize pheromones, as well as whether some mammalian V2Rs detect amino acids.

The Molecular Architecture of Detection

How does the olfactory system organize the signals provided by 1000 ORs and 200 VRs? In situ hybridization studies indicate that each OR gene is expressed in ~1/1000 OE neurons, suggesting that each neuron expresses only one OR gene (Nef et al., 1992; Strotmann et al., 1992; Ressler et al., 1993; Vassar et al., 1993; Chess et al., 1994). This was recently confirmed using single cell PCR (Malnic et al., 1999). Thus, information derived from different receptors is segregated, and the information that each neuron transmits to the brain is derived from only one receptor type.

There are four distinct spatial zones in the OE that express nonoverlapping sets of OR genes and project axons to different MOB zones (Ressler et al., 1993; Vassar et al., 1993; Strotmann et al., 1994; Sullivan et al., 1996) (Figure 1). The OE zones have the same membership and boundaries in different individuals, but their functions are unknown. Within a zone, neurons expressing the same OR are scattered, and neurons expressing different ORs are interspersed. Thus, sensory information is roughly organized into four large sets, but signals provided by each OR type are highly distributed over ~25% of the epithelial sheet.

In the VNO, the V1R and V2R genes show patterns of expression similar to those of OR genes in the OE (Figure 1). Here, there are two longitudinal zones, an upper zone that expresses V1Rs and the G protein Gαi2 and a lower zone that expresses V2Rs and the G protein Gαo (Dulac and Axel, 1995; Halpern et al., 1995; Berghard and Buck, 1996; Herrada and Dulac, 1997; Matsunami and Buck, 1997; Ryba and Tirindelli, 1997). Each VR gene is expressed in a small percentage of neurons, suggesting that each neuron expresses one VR gene, and neurons expressing the same VR are scattered in one zone. As in the OE, it appears that information is encoded in a distributed fashion in units defined by individual receptor types. With only one reported exception (Herrada and Dulac, 1997), VRs are similarly expressed in males and females, suggesting that sexually dimorphic pheromone responses may result from differences in brain neurocircuitry in males and females rather than from differing abilities to detect particular pheromones.

In the OE, ORs couple to the G protein Gαolf, which stimulates adenylyl cyclase III and an increase in cAMP that opens cyclic nucleotide-gated cation channels, causing membrane depolarization (Firestein, 1992; Reed, 1992; Brunet et al., 1996; Belluscio et al., 1999). Since VNO neurons lack most of these olfactory transduction molecules (Berghard et al., 1996), VRs must trigger transduction mechanisms involving different molecules. Although the mechanisms underlying VNO transduction are not yet clear, the G proteins Gαo and Gαi2 and the second messenger IP3 have been implicated in this process (Inamura et al., 1997; Krieger et al., 1999; Sasaki et al., 1999). In addition, Gαi2 and Gαo are both concentrated in the microvilli of VNO neurons, the presumed site of sensory transduction (Halpern et al., 1995; Berghard and Buck, 1996). A VNO-specific member of the Trp family of calcium channels is also concentrated in VNO microvilli, suggesting that it may somehow be involved as well. (Liman et al., 1999).

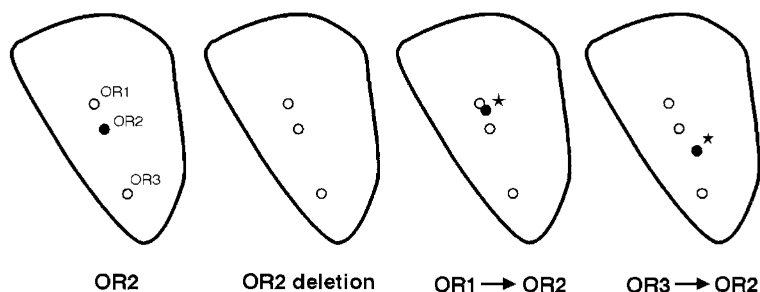
The Molecular Architecture of Inputs in the Olfactory Bulb

Studies of the patterns of axonal projections formed in the olfactory bulb by neurons expressing different ORs and V1Rs indicate that inputs derived from these receptors undergo a dramatic reorganization at this first brain relay (Figure 1). Differences between the patterns of inputs in the MOB and AOB also hint at possible differences in the processing of odor and pheromone signals.

Each OE neuron sends a single axon to the MOB where the axon synapses with the dendrites of bulb neurons in one of ~2000 glomeruli on the bulb surface (Shepherd, 1988; Kandel et al., 2000). Several thousand OE neurons synapse in each glomerulus. The pattern of inputs to the MOB from neurons expressing different ORs was first revealed by in situ hybridization (Ressler et al., 1994; Vassar et al., 1994). Individual OR probes labeled OE axons in 1–3 glomeruli at two sites, one on either side of the MOB. Different OR probes labeled different glomeruli, which had the same locations in different individuals. Subsequent studies that used gene targeting to coexpress a tau-lacZ fusion gene with a single OR gene allowed visualization of individual axons and showed that *all* axons of neurons expressing a given OR converge on the same glomeruli (Mombaerts et al., 1996; Wang et al., 1998). Thus, while OE neurons that express the same OR are scattered in one OE zone, their axons converge at two specific MOB sites, giving rise to a stereotyped sensory map in which inputs from different ORs are segregated in different glomeruli. Since mitral cell relay neurons in the MOB are each connected to one glomerulus, the segregation of inputs from different ORs seen in the OE and MOB is likely to be perpetuated in these cells and the signals that they transmit to the cortex as well.

The convergence of signals from thousands of neurons expressing the same OR onto a few glomeruli may optimize sensitivity to low concentrations of odorants by allowing the integration of weak signals from many OE neurons. The invariant pattern of inputs might have a different advantage, insuring that the neural representation, or "code," for an odorant remains constant over time, even though OE neurons are short-lived cells that are continuously replaced.

VNO axons synapse in the glomeruli of the AOB. The AOB resembles the MOB, but here each mitral cell is connected to multiple glomeruli as in the olfactory bulbs of lower vertebrates, such as fish (Takami and Graziadei, 1991). Recently, gene targeting was used to coexpress tau-lacZ with individual V1R genes (Belluscio et al., 1999; Rodriguez et al., 1999). In contrast to what had been seen in the MOB, the labeled axons of neurons expressing the same V1R converged in 10–30 glomeruli. Although the glomeruli appeared to be located in predictable subdomains of the AOB, their precise number and locations varied among individuals as well as in the two AOBs of the same individual. Interestingly, some



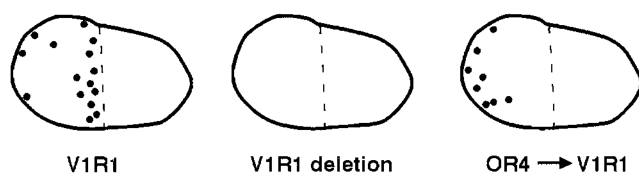


Figure 3. Altering the OR or V1R Expressed by a Sensory Neuron Changes Its Choice of Glomerular Targets in the MOB or AOB

MOB, glomerular targets of labeled axons when the coding region of the OR2 gene was unaltered (OR2), deleted (OR2 deletion), or replaced with the coding region of the OR1 or OR3 gene (OR1→OR2 or OR3→OR2). Normal targets of endogenous OR genes are shown as open circles. AOB, glomerular targets of labeled axons when the coding region of the V1R1 gene was unaltered (V1R1), deleted (V1R1 deletion), or replaced with the coding region of an OR gene (OR4→V1R1).

glomeruli contained both labeled and unlabeled axons, suggesting that they might receive input from neurons expressing different V1Rs, whereas this was not seen for one targeted OR in the MOB (Belluscio et al., 1999).

Do these differences between the AOB and MOB reflect significant differences in the way that odor and pheromone signals are processed? Possibly. In the moth, studies of a female mating pheromone indicate that it is composed of several chemicals that must be present in the correct proportions, a restriction apparently imposed by single relay neurons in the antennal lobe, the counterpart of the vertebrate olfactory bulb (Hildebrand and Shepherd, 1997). The integration of inputs from different V1Rs at the level of the AOB mitral cell could, by analogy, serve as a gate that restricts signal transmission to the amygdala to situations in which the correct combination of V1R inputs is achieved.

Development of the Signaling Architecture

The patterning seen at the first two levels of the odor and pheromone sensing pathways raises a number of questions about the mechanisms that shape the organization of the olfactory system during development. One question is how each OE or VNO neuron comes to express only one receptor gene for expression from a multitude of candidate receptor genes. The organization of OR gene expression in the OE suggests that the developing neuron arbitrarily selects one gene for expression from a specific zonal gene set comprised of several hundred OR genes. Chromosome mapping studies further indicate that genes expressed in the same zone can be found at many of the 12 or more OR gene loci in the genome (Sullivan et al., 1996). The mechanisms underlying OR gene choice are unknown. However, this, together with the ability of the 5′ flanking region of an OR to drive expression of a reporter gene in a subset of scattered OE neurons (Qasba and Reed, 1998), suggests that the choice may involve locus-independent mechanisms.

A second intriguing question is how the patterning of the OE-MOB projection is established. In zebrafish, differences have been seen in the onset of expression of different OR genes during development (Barth et al., 1996). However, in the mouse embryo, different ORs are first expressed around the same time, and this time precedes entry of OE axons into the MOB (Strotmann et al., 1995; Sullivan et al., 1995). This argues against a role for either temporal differences in the onset of expression of different ORs or retrograde signals from the MOB in setting up the projection. One might imagine that the zone–zone aspect of the projection involves guidance molecules that guide or restrict OE axons to a particular MOB zone (Tessier-Lavigne and Goodman, 1996). Two molecules differentially expressed in OE zones that might be involved in this process are Rb8 (OCAM) and CC2 (Schwob and Gottlieb, 1986; Schwarting and Crandall, 1991; Alenius and Bohm, 1997; Yoshihara et al., 1997).

A more perplexing problem is how sensory axons are targeted to specific glomeruli. Surprisingly, the receptor expressed by the sensory neuron appears to play a crucial role in glomerular targeting in both the MOB and AOB. The importance of the receptor in targeting was revealed by experiments that coexpressed a tau-lacZ fusion gene with individual OR or V1R genes whose coding regions were deleted or altered (Mombaerts et al., 1996; Wang et al., 1998; Belluscio et al., 1999; Rodriguez et al., 1999) (Figure 3). Deletion of an OR or V1R coding region disrupted axon targeting (Wang et al., 1998; Belluscio et al., 1999; Rodriguez et al., 1999). Instead of converging on specific glomeruli, the labeled axons were scattered in the AOB or MOB. A reduction in the number of labeled OE or VNO neurons suggested that expression of a functional receptor is also important for neuronal survival.

Although the effects of receptor deletion could be secondary to effects on survival, receptor "swap" experiments indicate that the receptor plays a more important

role, determining not just whether the neuron can form or maintain a synapse, but where it chooses to do so. When the coding region of one OR gene ("OR2") was replaced with that of an OR gene expressed in a different OE zone (OR3→OR2), the axons targeted to a novel glomerulus (Mombaerts et al., 1996), but when the two ORs were expressed in the same OE zone (OR1→OR2), the axons converged in a glomerulus adjacent to that normally targeted by neurons expressing the "donor" gene (OR1) (Wang et al., 1998) (Figure 3).

It is not yet known how the expressed OR influences the choice of target site or whether or not other types of molecules are involved. Two different mechanisms have been found to shape axonal projections in some other neural systems: axon guidance molecules that work by chemoattraction or chemorepulsion, and activity-dependent mechanisms, in which coincident activity in axons leads them to synapse with the same target neurons, presumably via feedback from the target neurons (Goodman and Shatz, 1993; Tessier-Lavigne and Goodman, 1996). Several findings argue against a role for activity-dependent mechanisms in glomerular targeting. First, OE axons target normally in mice that are unresponsive to odorants because they lack Gαolf (Belluscio et al., 1998). Second, glomerular targeting is normal in mutant mice that lack MOB neurons with which OE axons synapse (Bulfone et al., 1998). An alternative possibility is that the OR has a dual function, serving as a receptor for sensory stimuli in the OE and as an axon guidance molecule in the bulb. Surprisingly, replacement of the coding region of a V1R gene with the coding region of an OR gene allowed convergence onto a novel set of glomeruli in the AOB , a finding that is hard to explain in this context (Rodriguez et al., 1999) (Figure 3).

Molecular Codes for Odors

Recent studies have also begun to shed light on how the OR family is used to encode the identities of different odorants. The ligand specificities of cloned receptors are usually studied by expressing them in a heterologous cell type. With one exception (Raming et al., 1993), this method has not worked for ORs, because, unless they are structurally altered, they fail to reach the plasma membrane. Recently, three alternative methods have matched individual ORs with odorants, providing information about the molecular mechanisms underlying odor discrimination and the strategies used to encode the identities of different odors.

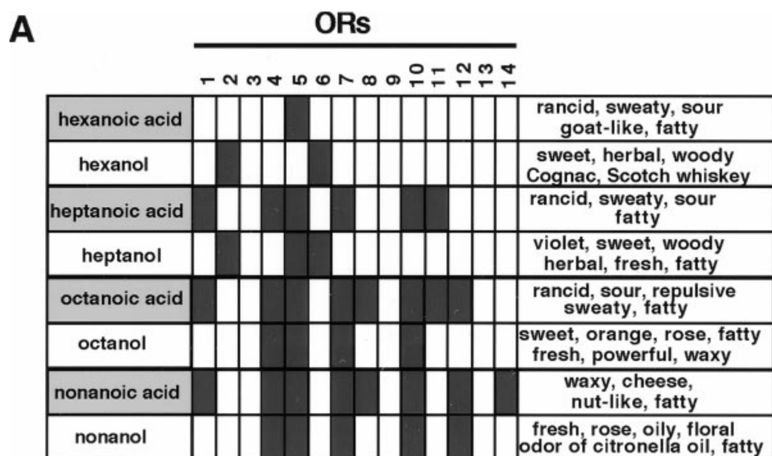
In one study, Zhao et al. (1998) infected the OE with an adenovirus containing an OR cDNA, allowing, for the first time, detailed analysis of the ligand specificity of a particular OR, rat OR-I7. Electrophysiological recordings of infected OE neurons showed that I7 recognizes octanal, and to a lesser extent heptanal and nonanal, but not 71 other related and unrelated odorants. Given that individual OE neurons can respond to multiple odorants (Sicard and Holley, 1984; Firestein et al., 1993; Sato et al., 1994; Bozza and Kauer, 1998) and OE neurons appeared likely to express one OR gene each (see above), it was expected that a single receptor might recognize more than one odorant, but this was the first analysis that directly showed how restricted a single OR can be in its recognition properties.

A second study showed that the addition of the N-terminal 20 amino acids of bovine rhodopsin to the N terminus of an OR allows surface expression of the OR in heterologous cells (Krautwurst et al., 1998). Using this method, it was shown that, remarkably, changing a single amino acid in transmembrane domain 5 of rat OR-I7 changes its primary ligand specificity from octanal to heptanal. This result was consistent with the idea that ligand binding occurs in a pocket formed by transmembrane domains and that the extreme variability of these domains is important to the diverse ligand specificities of ORs. By screening a library of chimeric receptors encoding the N and C terminal regions of one rhodopsin-tagged OR and the transmembrane domain 2–7 region of a large variety of ORs, this group went on to identify ORs for several different odorants, including one that could distinguish between the stereoisomers of one odorant. Attaching a signal sequence to the N terminus of an OR has similarly been found to allow its surface expression and ligand determination (Wetzel et al., 1999).

In a third approach to studying the functions of ORs, a combination of calcium imaging and single cell RT-PCR was used to identify ORs expressed by mouse OE neurons that respond to specific odorants (Malnic et al., 1999; Touhara et al., 1999). Importantly, both studies identified only one expressed OR gene per cell, and a series of control experiments ruled out contaminating DNA and other potential artifacts in the identification of the expressed OR (Malnic et al., 1999). In one study, the OR expressed in a neuron responsive to the odorant lyral was identified, and adenoviral-mediated expression of the OR in OE neurons confirmed its specificity (Touhara et al., 1999). In the other study, single neurons were tested with four classes of aliphatic odorants with the same carbon chains but different functional groups. In this study, individual ORs recognized multiple odorants and individual odorants were recognized by multiple ORs. However, different odorants were detected by different combinations of ORs, indicating that the OR family is used in a combinatorial fashion to encode the identities of different odorants. Even if each odorant were encoded by only three ORs, the number of odorants that could theoretically be discriminated by this scheme would be nearly one billion. These findings at the level of the OR family provide a mechanistic explanation for numerous previous observations that different odorants elicit activity in different combinations of mitral cells and glomeruli in the MOB (see below).

As with the I7 OR, most of the aliphatic ORs identified in this study detected only odorants with several consecutive carbon chain lengths. However, the 14 ORs identified varied extensively in their recognition properties, with different ORs recognizing odorants with different carbon chain lengths and different functional groups, or combinations of functional groups. In addition, individual odorants were detected by highly related as well as divergent ORs. This high level of recognition diversity provides a basis for the olfactory system's discriminatory capacity and its ability to detect odorants with a variety of different structures.

One remarkable feature of olfactory perception is that a slight alteration in the structure of an odorant can sometimes dramatically change in its perceived odor



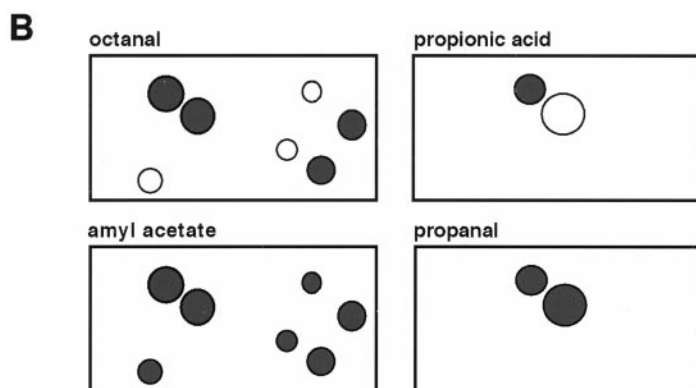


Figure 4. Different Odorants Are Detected by Different Combinations of ORs (A) and Activate Different Combinations of Glomeruli in a Segment of the Olfactory Bulb (B)

Filled circles indicate activated glomeruli (B).

(Beets, 1970). The aliphatic carboxylic acids used in this study all have unpleasant odors and are described, for example, as rancid, sweaty, or goat-like. In contrast, the aliphatic alcohols, which differ from the acids by a single functional group, are perceived as pleasant and have, for example, woody or orange scents. The combinations of ORs that recognized the acid and alcohol with the same carbon chain were invariably different in this study, even though many ORs recognized both (Figure 4A). Clearly, mice and humans may perceive these odorants differently. However, given that the same strategies are likely to be used in mouse and human to detect and discriminate odors, these findings suggest that changes in perception that accompany alternations in odorant structure may be a result of changes in the odorant's "receptor code." A change in odorant concentration, which can similarly alter perceived odor, was also found to result a change in receptor code, consistent with this idea.

Activity Codes for Odors

Numerous analyses of odor-induced activity in the MOB have shown that individual mitral cells and glomeruli can respond to multiple odorants and that a single odorant can elicit responses in multiple mitral cells or glomeruli that have characteristic locations, leading to the suggestion that different odorants are encoded by different combinations of MOB glomeruli (Kauer, 1987; Hildebrand and Shepherd, 1997; Mori et al., 1999). More recently, optical imaging techniques have been developed that allow odor responses to be visualized over large regions of the bulb in living animals and direct comparisons to be made of responses to a variety of odorants in both lower (Cinelli and Kauer, 1992; Friedrich and Korsching, 1997) and higher (Rubin and Katz, 1999) vertebrates. In each case, odorant responses appear to be combinatorial, with different combinations of glomeruli responding to different odorants.

In a recent study in rat that used imaging of intrinsic signals to examine MOB responses to aliphatic aldehydes and other odorants individual glomeruli responded to odorants with several consecutive carbon chain lengths, and partially overlapping sets of glomeruli responded to different odorants (Rubin and Katz, 1999) (Figure 4B). In addition, increasing odorant concentrations led to increases in the number of responsive glomeruli. As already discussed, these features were also seen in studies of OR odorant specificities and are consistent with the apparent innvervation of each glomerulus by neurons that all express the same OR.

Beyond the Olfactory Bulb

It is not yet known how signals derived from different ORs and VRs are organized beyond the bulb, nor is it

known how those signals are ultimately decoded to yield the perception of an odorant or a specific endocrine or behavioral response to a pheromone. It was recently shown that a truncated form of wheat germ agglutinin or its close relative, barley lectin, can serve as a transneuronal tracer when it is expressed from a transgene in mice (Horowitz et al., 1999; Yoshihara et al., 1999). Studies in which one of these lectins is coexpressed with a single OR or VR should allow for visualization of the patterns of inputs formed at higher levels of the odor and pheromone sensing pathways. Imaging studies should also provide important insight into the roles played by the intrinsic circuitry of the olfactory bulb and subsequent relays in the final readout of odor and pheromone signals.

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