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64. I thank L. Buck and R. Axel for initiating this journey, and R. Axel for postdoctoral guidance and continuous support. I thank the members of my laboratory, in particular T. Bozza and C. Zheng, and S. Firestein for critically reviewing the manuscript. I benefited from incisive comments by T. Perry and L. Stryer. I thank C. Bargmann, J. Carlson, P. Sengupta, E. Troemel, and L. Vosshall for providing useful information. Supported by NIH and the Human Frontier Science Program. I am an Alfred P. Sloan, Basil O'Connor, Guggenheim, Irma T. Hirschl, Klingenstein, McKnight, Rita Allen, and Searle Scholar or Fellow.

REVIEW

The Olfactory Bulb: Coding and Processing of Odor Molecule Information

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Olfactory sensory neurons detect a large variety of odor molecules and send information through their axons to the olfactory bulb, the first site for the processing of olfactory information in the brain. The axonal connection is precisely organized so that signals from 1000 different types of odorant receptors are sorted out in 1800 glomeruli in the mouse olfactory bulb. Individual glomerular modules presumably represent a single type of receptor and are thus tuned to specific molecular features of odorants. Local neuronal circuits in the bulb mediate lateral inhibition among glomerular modules to sharpen the tuning specificity of output neurons. They also mediate synchronized oscillatory discharges among specific combinations of output neurons and may contribute to the integration of signals from distinct odorant receptors in the olfactory cortex.

The sensory input to the olfactory system is mediated by odor molecules that represent an amazingly diverse range of structure. How can the mammalian olfactory system detect and discriminate such a large variety of odor molecules? Recent studies have begun to elucidate the molecular and cellular mechanisms for the reception of odor molecules at the level of olfactory sensory neurons in the nose (*1–5*). To cope with the diverse odor molecules, mammals have developed up to 1000 odorant receptors (*3, 4, 6*), which are expressed on the cilial membrane surface of sensory neurons in the olfactory epithelium (OE).

The central olfactory system receives the odor molecule information through axons of sensory neurons. The information is processed and integrated as the olfactory quality of objects. The human perception of the olfactory image is characteristic in that it usually associates with pleasant or unpleasant emotions. Because a single object, such as the flower of jasmine, emits a specific combination of dozens of different odor molecules, the central olfactory system has to integrate signals from a large variety of odorant receptors. This poses an interesting but daunting question as to how the central olfactory system combines or compares signals among 1000 types of odorant receptors. Recent progress has begun to unravel the basic cellular mechanisms for processing the molecular information at the first relay station of the central olfactory system, the main olfactory bulb (MOB) (*7*).

The mammalian MOB has a relatively simple cortical structure, containing thousands of signal-processing modules called

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"glomeruli" (*8*). Glomeruli are relatively large spherical neuropils (100 to 200 μm in diameter), within which axons of olfactory sensory neurons form excitatory synaptic connections on dendrites of mitral and tufted cells, the output neurons of the MOB (*9*) (Fig. 1). An individual glomerulus can be viewed as an olfactory axon convergence center for inputs originating from one type of odorant receptor; the odorant receptor–specific signal is transmitted to mitral and tufted cells innervating the glomerulus. In mice, each glomerulus receives converging axonal inputs from several thousand olfactory sensory neurons and is innervated by primary dendrites of ~20 mitral cells (*10*) (Fig. 1). If we refer to a glomerulus together with its associated neurons as a glomerular module, the architecture of the mouse MOB can be simplified as being composed of 1800 such modules. The odor molecule information is processed by the local neuronal circuits that mediate synaptic interactions within the module as well as among these modules in the MOB. Axons of mitral and tufted cells then send the information to the olfactory cortex (Fig. 1).

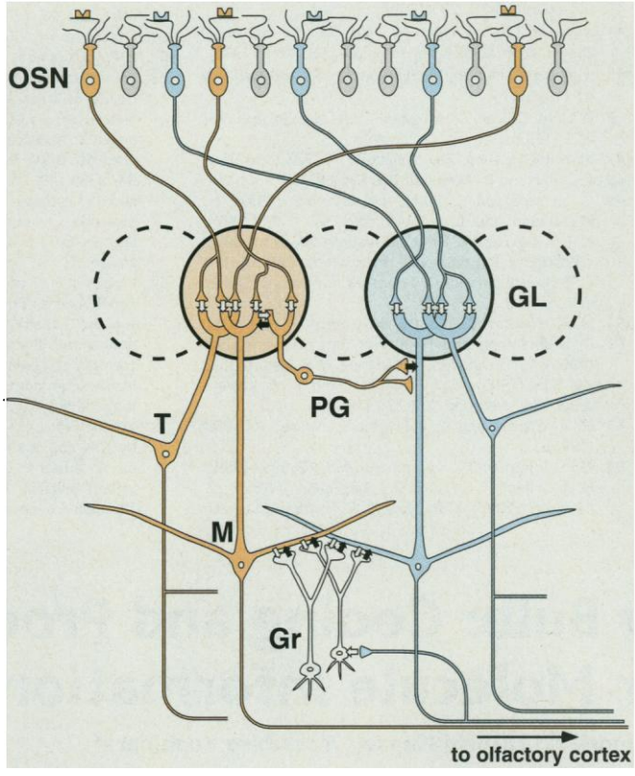

Fig. 1. Basic circuit diagram summarizing the synaptic organization of the mammalian MOB. Two glomerular modules (brown and blue) represent two different types of odorant receptors. Mitral cells (M) and tufted cells (T) are output neurons, and granule cells (Gr) and periglomerular cells (PG) are local interneurons. OSN, olfactory sensory neuron; GL, glomerulus. Short white arrows denote excitatory synapses, and short black arrows denote inhibitory synapses.

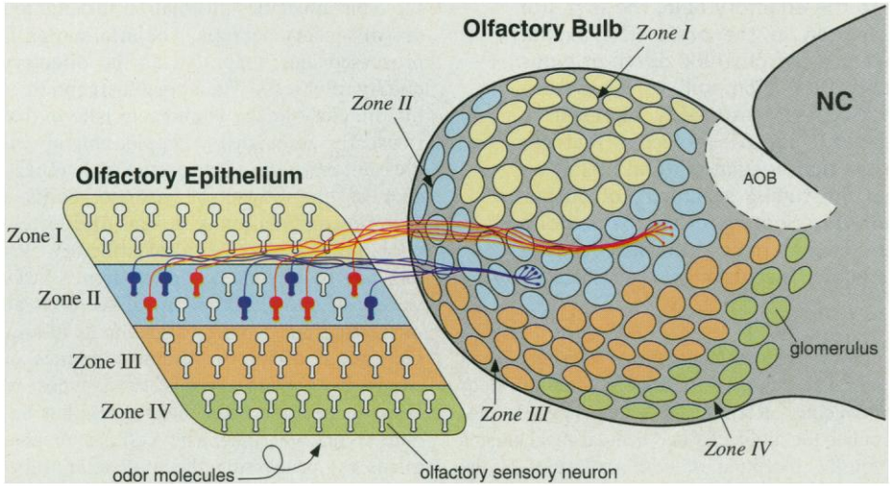

Fig. 2. Schematic diagram illustrating the axonal connectivity pattern between the nose and the MOB. The OE in mice is divided into four zones (zones I through IV) that are defined by the expression of odorant receptors. Olfactory sensory neurons in a given zone of the epithelium project to glomeruli located in a corresponding zone (*zones I* through *IV*) of the MOB. Axons of sensory neurons expressing the same odorant receptor (red or dark blue) converge to only a few defined glomeruli. NC, neocortex; AOB, accessory olfactory bulb.

Axonal Connection Between Nose and Olfactory Bulb

In mice, the OE contains more than 2 million sensory neurons. Individual olfactory sensory neurons express only one type of odorant receptor gene (*11–13*) out of a repertoire of up to 1000 genes. This suggests that individual sensory neurons respond to a range of odor ligands that bind to the expressed receptor (*13–15*). However, it is still unknown as to which range of odor molecules individual sensory neurons are tuned to (*13–16*). Each neuron projects a single axon into a single glomerulus in the MOB. How is the axonal connection functionally organized between the OE and the MOB? Two basic principles of the olfactory axon projection have been demonstrated: "zone-to-zone projection" and "glomerular convergence."

Zone-to-zone projection. Odorant receptors are classified into four groups, according to their expression patterns in the OE. A given type of odorant receptor is expressed in one of four circumscribed zones in the OE (*12, 17*) (Fig. 2) (zones I, II, III, and IV are arranged from dorsomedial to ventrolateral parts of the OE) (OE zones are given in roman type, and MOB zones are given in italic type). Within a given zone, neurons expressing different receptors intermingle, showing widely dispersed distribution. Structural comparison of various odorant receptors, in relation to their expression zones, revealed that the odorant receptors with highly homologous amino acid sequences tended to be localized in the same zone of the OE (*13*).

Such zonal organization is preserved to some extent in the MOB. The presence of zones in the glomerular sheet of the MOB was first shown in rabbits (*18*) and then in rats (*19*) with immunohistochemical studies using R4B12 and RB-8 antibodies, respectively. The antigen molecule recognized by these antibodies turned out to be a cell adhesion molecule, OCAM/RNCAM (*20*), which is expressed by axons of olfactory sensory neurons in zones II, III, and IV of the OE. Axons of zone I sensory neurons do not express OCAM. Tracing of OCAM-expressing olfactory axons to their terminals in the glomeruli showed zonally segregated projections of olfactory axons; OCAM-negative zone I axons project to

glomeruli in the rostrodorsal *zone I* of the MOB, whereas OCAM-positive zones II, III, and IV axons project selectively to caudoventral *zones II*, *III*, and *IV* of the MOB (Fig. 2). A complementary pattern was reported in the expression of CC2 carbohydrate epitope, which is only positive for zone I axons (*21*). Although molecular markers that distinguish glomeruli among *zones II*, *III*, and *IV* are still lacking, in situ hybridization studies of MOB sections with odorant receptor probes (*22*), together with studies of anatomical tracing of olfactory axons (*23*), suggest that the MOB may comprise four spatially segregated zones corresponding to the four zones in the OE. Thus, odor information received by sensory neurons in a given zone of the OE is thought to be transmitted to glomeruli and then transferred to mitral and tufted cells in the corresponding zone of the MOB.

Glomerular convergence. The olfactory axons can find their specific target glomeruli in the MOB. Recent studies have unraveled the highly ordered glomerular convergence pattern of olfactory axon projection: Olfactory sensory neurons expressing a given odorant receptor converge their axons onto a few defined glomeruli (Fig. 2).

Physiological studies had suggested the glomerular convergence pattern as one of the plausible models for explaining the tuning specificity of olfactory bulb neurons (*24–27*). The glomerular convergence has been visualized by two types of experiments. In situ hybridization analysis showed the presence of odorant receptor messenger RNA (mRNA) in the olfactory axon terminals in glomeruli, indicating that the sensory neurons expressing a given odorant receptor mRNA converge their axons to particular glomeruli (*22*). Evidence that is more conclusive of the glomerular convergence was presented by using a gene-targeting technique, knock in, a method of replacing a particular gene with another gene construct (*28–30*).

Tuning of Individual Glomerular Modules to Specific Molecular Features

The glomerular convergence does not necessarily indicate that all olfactory axons converging onto a single glomerulus derive from the same type of sensory neurons expressing the same type of odorant receptor. It is possible that individual glomeruli receive mixed inputs from multiple types of odorant receptors. This issue was examined in the P2 odorant receptor–IRES-tauLacZ knock-in mice (IRES, internal ribosomal entry site) (*30*). In these mice, all olfactory axons innervating the P2 glomerulus expressed β-galactosidase, indicating that the P2 glomerulus receives olfactory axon inputs exclusively from sensory neurons expressing the P2 odorant receptor (*31*). With an extrapolation of this result, it appears likely that each glomerulus is devoted to a single odorant receptor. However, the "one glomerulus–one receptor" hypothesis needs to be examined experimentally for each glomerulus, and it is possible that convergence of inputs from multiple types of receptors occurs in some glomeruli of the MOB.

Functional importance of the glomerular convergence was examined with physiological methods (*32*), including single-unit recordings of spike responses from mitral and tufted cells to odor molecules (*24–26, 33*). Because individual mitral and tufted cells project a single primary dendrite to a single glomerulus, the tuning specificity of given mitral and tufted cells strongly reflects that of the glomerulus they innervate.

Detailed characterization of the tuning specificity of individual mitral and tufted cells was obtained in the rabbit MOB using a battery of odor molecules with systematic variations of molecular conformation (*25, 26*). The results demonstrated that single mitral and tufted cells show excitatory spike responses to a range of odor molecules with similar molecular conformation (Fig. 3). In other words, the molecular receptive range (MRR) (*26, 27, 34*) of individual mitral and tufted cells consists of a range of odor molecules that share characteristic structural features. The characteristic features include (i) the overall stereochemical structure of the hydrocarbon chain (Fig. 3) and (ii) the type and position of the attached functional group. These characteristics of odor molecules are similar to epitopes in the antigen-antibody interactions in the immune system (*35*) and are thus called "odotopes" (*36*). In agreement with the single-unit studies, optical imaging of odorant responses in rat MOBs showed that glomeruli were tuned to detect particular molecular features (*37*).

Mitral and tufted cells that presumably belong to different glomerular modules show different MRRs (*25–27*). The MRRs of two mitral cells located in the ventromedial part of the rabbit MOB are shown in Fig. 3. The mitral cell in Fig. 3A discriminates among different stereochemical isomers of disubstituted benzenes and is tuned selectively to detect those odor molecules that have two side chains in para position. However, the mitral cell in Fig. 3B does not discriminate among different isomers and is tuned to detect disubstituted benzenes that have short side chains in any position (ortho, meta, or para). This suggests that different glomerular modules are tuned to detect different molecular features. In Fig. 3, the odor molecule "*para*-xylene" (shown by an asterisk) is detected by both mitral cells, presumably because it is para-isoform with short side chains.

An individual glomerular module can thus be viewed as a molecular feature–detecting unit. Because an individual odor molecule typically exhibits several molecular features, it may activate a specific combination of the molecular feature–detecting units. This is supported by the results of spatial mapping of glomerular activity after stimulation of the OE with a

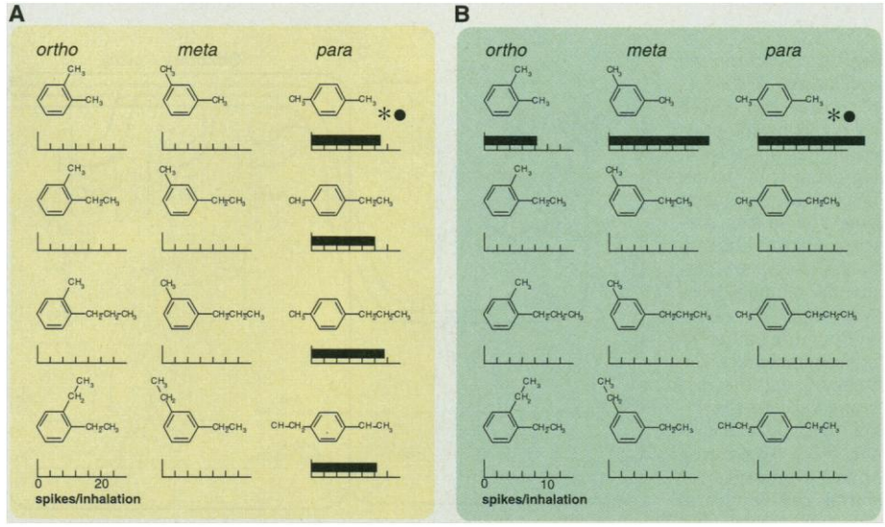

Fig. 3. Different glomerular modules detect different molecular features. Response specificity of two mitral cells (**A** and **B**) to a number of odor molecules made of isomeric disubstituted benzenes. Solid bars indicate the mean number of spikes per inhalation cycle elicited by stimulation with respective odor molecules. The molecular structure of odor molecules is shown above each graph. The neuron in (A) is tuned selectively to para-isomers of disubstituted benzenes, whereas the neuron in (B) responds selectively to disubstituted benzenes with short side chains. Asterisks indicate *para*-xylene, which in this case activates both neurons. Modified from (*26*).

single odor compound as measured by 2-deoxyglucose uptake, c-*fos* expression, functional magnetic resonance imaging, and optical imaging (*37–39*). The quality of an individual odor molecule is thus coded by a combination of activated glomerular modules. This is also the case for a mixture of odor molecules; dozens of odor molecules released from a particular object may activate a selective set of glomerular modules. Regardless of the complexity of odor molecules emitted from a given object, its olfactory quality may be coded by a specific combination of activated glomerular modules at the level of the MOB.

Spatial Arrangement of Glomerular Modules in the MOB

How are the glomerular modules spatially arranged in the MOB? Glomeruli are parceled into four zones in the MOB (Fig. 2). Examination of tuning specificity of mitral and tufted cells suggests that glomeruli representing odorant receptors with similar tuning specificity are assembled in a local region within a specific zone. For example, mitral and tufted cells in the dorsomedial region in *zone I* of the rabbit MOB show similar MRRs covering *n*-fatty acids or *n*-aliphatic aldehydes or both. In contrast, these neurons rarely respond to *n*-aliphatic alcohols, and they never respond to alkanes (*24, 25, 27*). Glomeruli or mitral and tufted cells in a given region show varying overlapping MRRs (*15, 27, 37*). The local assembly of glomerular modules with varying overlapping specificities to odor molecules seems to be crucial for processing molecular information in the MOB.

An integration into a coherent map of the results of spatial arrangement of glomeruli obtained from in situ hybridization studies (*22*) and odorant receptor-tauLacZ studies (*28, 29*) suggests that each MOB represents two symmetrical sensory maps of odorant receptors, one in the lateral hemisphere and the other in the medial hemisphere of the MOB. The idea of two symmetrical maps is in agreement with mediolateral symmetric distribution of 2-deoxyglucose uptake foci after stimulation with particular odor molecules (*2, 38*). The functional meaning of the possible dual sensory maps in the MOB remains to be elucidated.

Interaction Among Molecular Feature–Detecting Glomerular Modules

The glomerular modules in the MOB interact with each other through neuronal circuits by local interneurons, granule cells, and periglomerular cells. Mitral and tufted cells project secondary dendrites tangentially for long distances and make numerous dendrodendritic reciprocal synapses with granule cell dendrites (Fig. 1). The reciprocal synapse consists of a mitral-to-granule glutamate-mediated excitatory synapse and a granule-to-mitral γ-aminobutyric acid–mediated inhibitory synapse (*8, 40*). Thus, activation of a mitral and tufted cell results in feedback inhibition of the cell, as well as lateral inhibition of neighboring mitral and tufted cells (*8, 40, 41*). The primary dendrites of mitral and tufted cells form dendrodendritic reciprocal synapses with periglomerular cells within the glomerulus. Some of the periglomerular cells send inhibitory projections to the dendrites of neighboring mitral and tufted cells, suggesting that periglomerular cells also provide lateral inhibition of mitral and tufted cells. Accumulating evidence suggests that interactions among mitral and tufted cells through these interneurons play a central role in the processing of olfactory information (*33, 42, 43*).

Enhancement of tuning specificity by lateral inhibition. Of particular interest is the lateral inhibition mechanism by which activation of mitral and tufted cells associated with one glomerular module results in the inhibition of mitral and tufted cells associated with neighboring glomerular modules (*8, 33, 44*). Single-unit recordings from mitral and tufted cells in the rabbit MOB showed that spike activity of an individual cell is inhibited by a defined subset of odor molecules with structure that is closely related to the excitatory odor molecules (*26, 42*). A pharmacological blockade of the dendrodendritic synapses between mitral/tufted and granule cells greatly reduces the odor-induced lateral inhibition. The lateral inhibition through the dendrodendritic reciprocal synapses with granule cells may enhance the contrast between strongly activated and faintly activated glomeruli and thus sharpen the tuning specificity of individual mitral and tufted cells to odor molecules. The second-order mitral and tufted cells may thus be more sharply tuned to specific molecular features than olfactory sensory neurons are (*34, 42*).

Synchronized oscillatory discharges of mitral and tufted cells and binding of different glomerular modules. At the level of the MOB, the quality of stimulus odor is encoded by a specific combination of activated glomerular modules. How does the local neuronal circuit in the MOB contribute to the combination and integration of signals received by different glomerular modules? A recent physiological study (*43*) raised the possibility that the local neuronal circuit generates synchronized oscillatory discharges (*45*) of bulbar output neurons, mitral and tufted cells, thereby contributing to the combining of signals from different glomerular modules at the level of olfactory cortex (Fig. 4). Synchronized oscillatory discharges are thought to play an important role in the insect central olfactory system (*46*).

Inhalation of odor molecules elicits a prominent oscillation (30 to 80 Hz) of local field potentials (*47*), imply that many mitral and tufted cells respond with synchronized spike discharges. Dendrodendritic synaptic connections between mitral/tufted cells and granule cells are thought to be responsible for generating the oscillatory local field potentials (*8, 40, 48*). Simultaneous recordings from two mitral/tufted cells located 300 to 500 μm apart (*43*) showed that synchroniza-

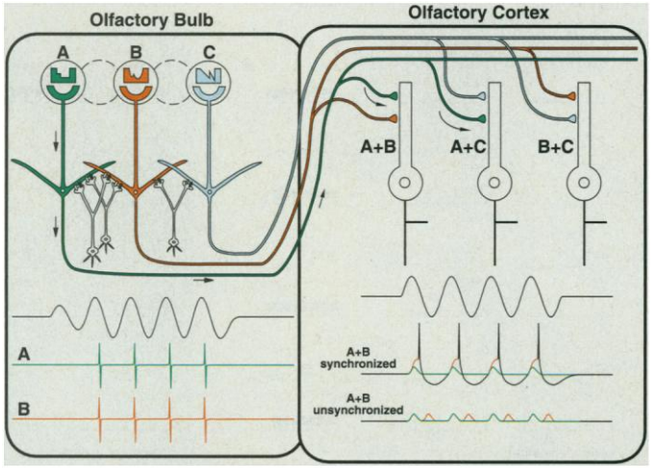

Fig. 4. Synchronized oscillatory discharges of mitral and tufted cells and presumptive combination-detecting neurons in the olfactory cortex. **(Left)** The schematic diagram of the olfactory bulb shows three glomerular modules (cells A through C) representing three different odorant receptors. The traces under the diagram indicate the local field potential in the MOB (top trace), spike discharges of mitral cell A (green) (middle trace) and spike discharges of mitral cell B (orange) (bottom trace). Spike discharges are synchronized between cells A and B. **(Right)** Diagram of the olfactory cortex indicates presumptive convergence of mitral cell axons onto individual cortical neurons. The traces indicate oscillatory local field potential in the olfactory cortex (top trace), synaptic and spike potentials in the hypothetical cortical neuron (A + B) when the inputs are synchronized (middle trace), and synaptic potentials when the inputs are unsynchronized (bottom trace). In the middle trace, temporal summation of synaptic inputs from mitral cells A and B gives rise to spike discharges of this cortical neuron.

tion of spike discharges occurs during odor stimulation among specific pairs of mitral/tufted cells that are associated with different glomerular modules (Fig. 4, left); a clear synchronization was observed in about one-fourth of the mitral and tufted cells examined.

If axons of two mitral/tufted cells belonging to different glomerular modules converge onto the same target neuron in the olfactory cortex, the cortical neuron may serve as a combination detector whose activity represents combined activation of the two glomerular modules (Fig. 4). Synchronization of spike discharges of the bulbar output neurons may greatly enhance the probability of driving the target cortical neuron because of the temporal summation of synaptic inputs from the two mitral/tufted cells (the trace shown by A + B synchronized in Fig. 4, right). Thus, synchronization of two mitral/tufted cells associated with different glomerular modules might serve as a mechanism for the temporal binding of signals from different odorant receptors. During inhalation of odor molecules emitted from a specific object, synchronized spike responses may occur in a number of mitral and tufted cells associated with a specific subset of glomeruli representing a selective combination of odorant receptors.

The above discussion leads to the hypothesis that the strength of the dendrodendritic reciprocal synaptic connections with granule cells that bridge two different mitral/tufted cells may determine the degree of spike synchronization. If this is the case, dendrodendritic reciprocal synapses can serve as a substrate for mediating the temporal and functional binding of signals from different odorant receptors. Of particular interest is the possibility that a plastic change in the strength of the dendrodendritic synapses may result in a change in the strength of the functional binding of signals among different odorant receptors. It has been suggested that at least a part of olfactory or pheromonal (or both) memory trace resides in the dendrodendritic reciprocal synapses (*49*). One of the basic mechanisms for olfactory memory might be to change the strength of the dendrodendritic synaptic connections among specific subsets of mitral and tufted cells. This may cause changes in the efficacy of driving selective subsets of odorant receptor combination–detecting neurons in the olfactory cortex.

Conclusion

The finding of a large multigene family of odorant receptors (*6*) has triggered rapid advances concerning the functional organization of the mammalian olfactory nervous system. The initial step was an understanding of the functional roles of individual sensory neurons in the OE. Next came the elucidation of the axonal projection patterns of sensory neurons to the MOB. This led to the notion that the functional logic for discrimination among different odor molecules is determined by the pattern of olfactory axon connectivity to the MOB, the glomerular convergence. We now know of the following neuronal mechanisms for the processing of odor molecule information in the MOB: (i) Individual glomerular modules function as a molecular feature–detecting unit, and (ii) local neuronal circuits mediate lateral inhibition and synchronized spike discharges among mitral and tufted cells that belong to different glomerular modules.

However, we still lack basic knowledge of the detailed functional organization of the axonal projection of mitral and tufted cells to the olfactory cortex and of the neuronal circuits in the olfactory cortex (*50*). Thus, the challenge is to understand neuronal mechanisms as to how the olfactory cortex combines or compares signals from 1800 glomerular modules. Newly developed techniques, including transsynaptic labeling of selective neuronal pathways by plant lectin transgenes (*51*), might provide a clue for understanding the axonal connectivity pattern between the MOB and the olfactory cortex. When our knowledge of the olfactory cortex and higher olfactory centers advances, we might be able to determine why roses have a pleasant scent, whereas sweaty socks smell bad.

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52. This work was supported in part by a grant from the Human Frontier Science Program; by a grant from the Ministry of Education, Science, Sports, and Culture of Japan; and by the Special Coordination Funds for Promoting Science and Technology from the Science and Technology Agency of Japan.

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