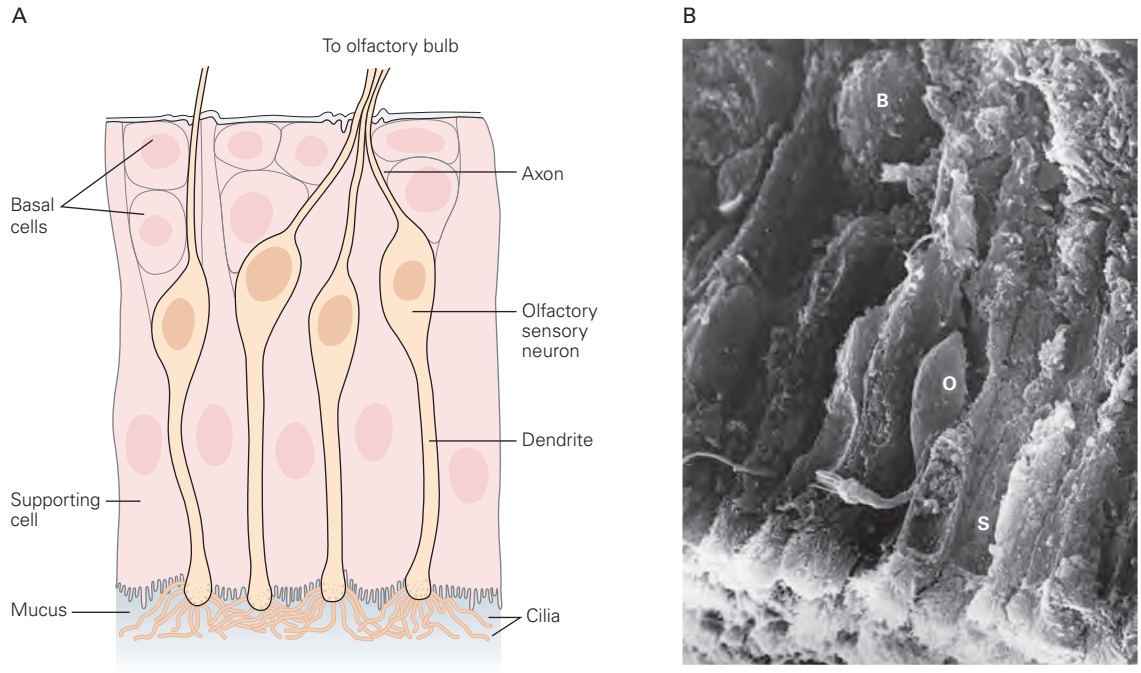

Figure 29–2 The olfactory epithelium.

A. The olfactory epithelium contains sensory neurons interspersed with supporting cells as well as a basal layer of stem cells. A single dendrite extends from the apical end of each neuron; sensory cilia sprout from the end of the dendrite into the mucus lining the nasal cavity. An axon extends from the basal end of each neuron to the olfactory bulb.

B. A scanning electron micrograph of the olfactory epithelium shows the dense mat of sensory cilia at the epithelial surface. Supporting cells (**S**) are columnar cells that extend the full depth of the epithelium and have apical microvilli. Interspersed among the supporting cells is an olfactory sensory neuron (**O**) with its dendrite and cilia, and a basal stem cell (**B**). (Reproduced, with permission, from Morrison and Costanzo 1990. Copyright © 1990 Wiley-Liss, Inc.)

thin cilia that protrude into the mucus that coats the nasal cavity (Figure 29–2). The cilia contain the odorant receptors as well as the transduction machinery needed to amplify sensory signals from the receptors and transform them into electrical signals in the neuron's axon, which projects from the basal pole of the neuron to the brain. The axons of olfactory sensory neurons pass through the cribriform plate, a perforated region in the skull above the nasal cavity, and then terminate in the olfactory bulb (see Figure 29–1).

Mammals Share a Large Family of Odorant Receptors

Odorant receptors are proteins encoded by a multigene family that is evolutionarily conserved and found in all vertebrate species. Humans have approximately 350 different odorant receptors, whereas mice have approximately 1,000. Although odorant receptors belong to the G protein–coupled receptor superfamily, they share sequence motifs not seen in other superfamily members. Significantly, the odorant receptors vary considerably in amino acid sequence (Figure 29–3A).

Like other G protein–coupled receptors, odorant receptors have seven hydrophobic regions that are likely to serve as transmembrane domains (Figure 29–3A). Detailed studies of other G protein–coupled receptors, such as the β-adrenergic receptor, suggest that odorant binding occurs in a pocket in the transmembrane region formed by a combination of the transmembrane domains. The amino acid sequences of odorant receptors are especially variable in several transmembrane domains, providing a possible basis for variability in the odorant binding pocket that could account for the ability of different receptors to recognize structurally diverse ligands.

A second, smaller family of chemosensory receptors is also expressed in the olfactory epithelium. These receptors, called trace amine-associated receptors (TAARs), are G protein–coupled, but their protein sequence is unrelated to that of odorant receptors. They are encoded by a small family of genes present in humans and mice as well as fish. Studies in mice, which have 14 different olfactory TAARs, indicate that TAARs recognize volatile amines, one of which is present in high concentrations in the urine of male

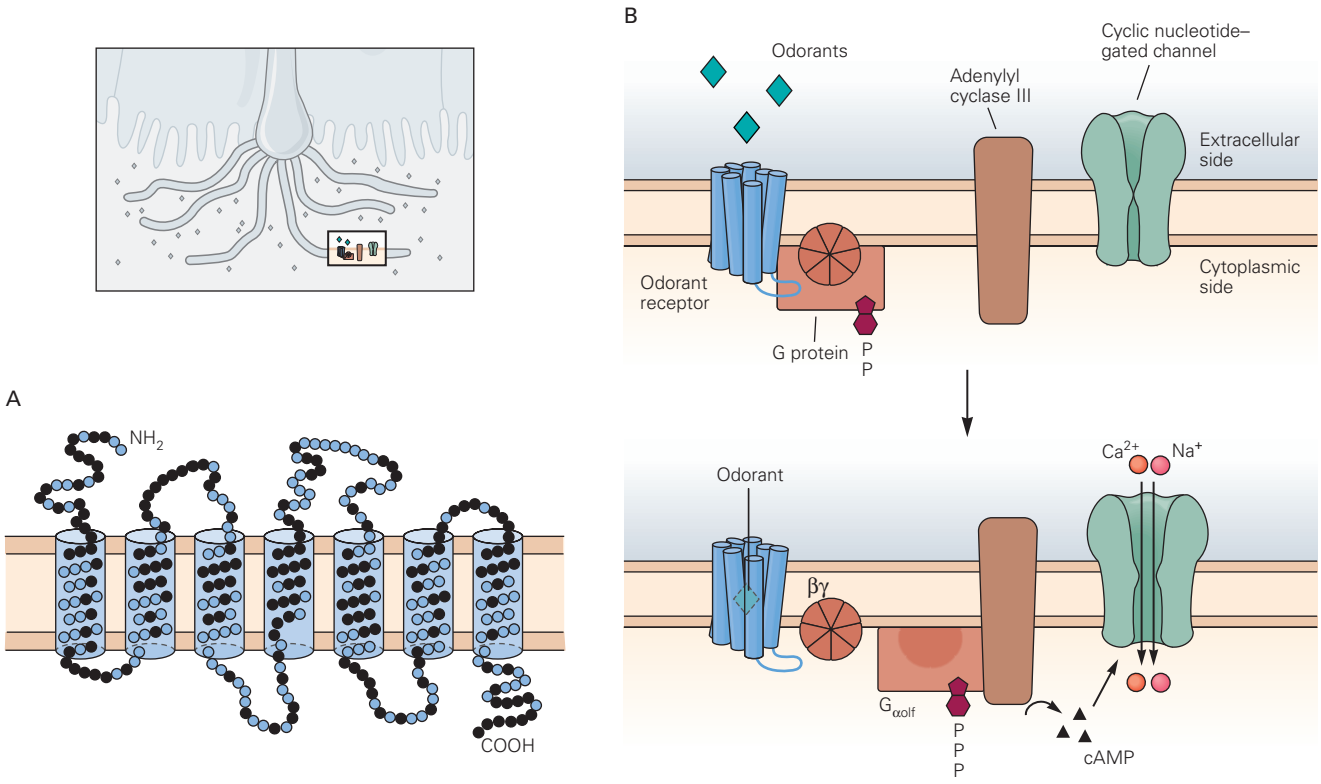

Figure 29–3 Odorant receptors.

A. Odorant receptors have the seven transmembrane domains characteristic of G protein–coupled receptors. They are related to one another but vary in amino acid sequence (positions of highest variability are shown here as **black balls**). (Reproduced, with permission, from Buck and Axel 1991.)

B. Binding of an odorant causes the odorant receptor to interact with $G\alpha_{olf}$, the α-subunit of a heterotrimeric G protein. This causes the release of a guanosine triphosphate (GTP)-coupled $G\alpha_{olf}$, which stimulates adenylyl cyclase III, leading to an increase in cyclic adenosine monophosphate (**cAMP**). The elevated cAMP in turn induces the opening of cyclic nucleotide–gated cation channels, causing cation influx and a change in membrane potential in the ciliary membrane.

mice and another in the urine of some predators. It is possible that this small receptor family has a function distinct from that of the odorant receptor family, perhaps one associated with the detection of animal cues. Another family of 12 receptors, called MS4Rs, is also found in mice, where it may be involved in the detection of pheromones and certain food odors.

The binding of an odorant to its receptor induces a cascade of intracellular signaling events that depolarize the olfactory sensory neuron (Figure 29–3B). The depolarization spreads passively to the cell body and then the axon, where action potentials are generated that are actively conducted to the olfactory bulb.

Humans and other animals rapidly accommodate to odors, as seen for example in the weakening of detection of an unpleasant odor that is continuously present. The ability to sense an odorant rapidly recovers when the odorant is temporarily removed. The adaptation to odorants is caused in part by modulation of a cyclic nucleotide–gated ion channel in olfactory cilia, but the mechanism by which sensitivity is speedily restored is not yet understood.

Different Combinations of Receptors Encode Different Odorants

To be distinguished perceptually, different odorants must cause different signals to be transmitted from the nose to the brain. This is accomplished in two ways. First, each olfactory sensory neuron expresses only one odorant receptor gene and therefore one type of receptor. Second, each receptor recognizes multiple odorants, and conversely, each odorant is detected by multiple different receptors (Figure 29–4). Importantly, however, each odorant is detected, and thereby encoded, by a unique combination of receptors and thus causes a distinctive pattern of signals to be transmitted to the brain.

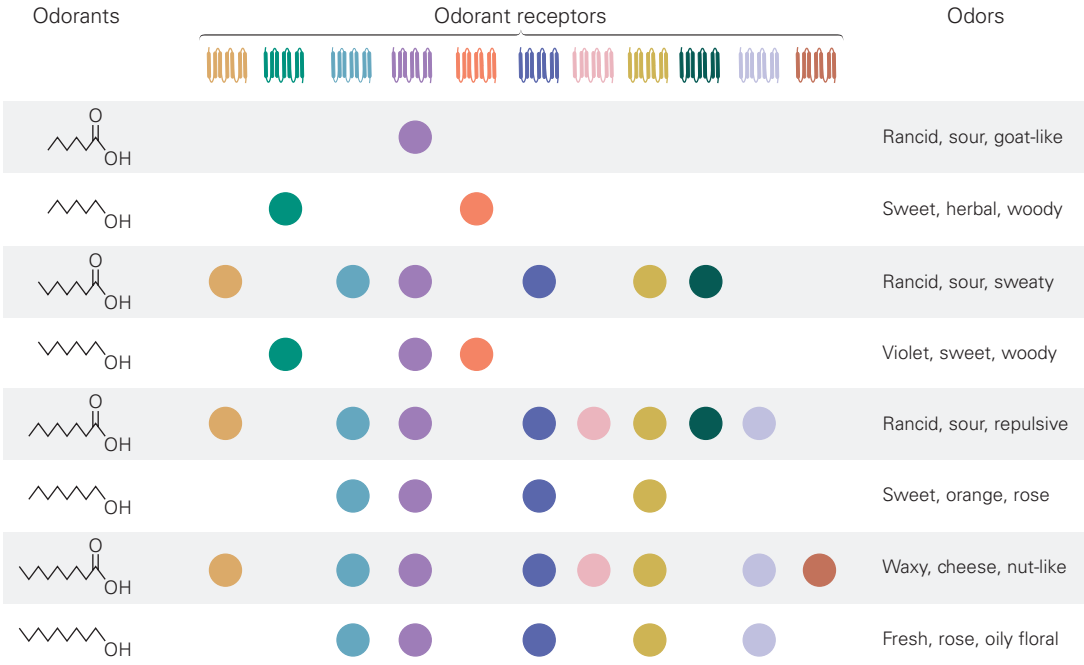

Figure 29–4 Each odorant is recognized by a unique combination of receptors. A single odorant receptor can recognize multiple odorants, but different odorants are detected, and thus encoded, by different combinations of receptors. This combinatorial coding explains how mammals can distinguish odorants with similar chemical structures as having different scents. The data in the figure were obtained by testing mouse olfactory sensory neurons with different odorants and then determining the odorant receptor gene expressed by each responsive neuron. The perceived qualities of these odorants in humans shown on the right illustrate how highly related odorants can have different scents. (Adapted, with permission, from Malnic et al. 1999.)

The combinatorial coding of odorants greatly expands the discriminatory power of the olfactory system. If each odorant were detected by only three different receptors, this strategy could in theory generate millions of different combinatorial receptor codes—and an equivalently vast number of different signaling patterns sent from the nose to the brain. Interestingly, even odorants with nearly identical structures are recognized by different combinations of receptors (Figure 29–4). The fact that highly related odorants have different combinatorial receptor codes explains why a slight change in the chemical structure of an odorant can alter its perceived odor. In some cases, the result is dramatic, for example, changing the perception of a chemical from rose to sour.

A change in concentration of an odorant can also change the perceived odor. For example, a low concentration of thioterpineol smells like tropical fruit, whereas a higher concentration smells like grapefruit and an even higher concentration smells putrid. As the concentration of an odorant is increased, additional receptors with lower affinity for the odorant are recruited into the response and thus change the combinatorial receptor code, providing an explanation for the effects of odorant concentration on perception.

Olfactory Information Is Transformed Along the Pathway to the Brain

Odorants Are Encoded in the Nose by Dispersed Neurons

How are signals from a large array of different odorant receptors organized in the nervous system to generate diverse odor perceptions? This question has been investigated in rodents. Studies in mice have revealed that olfactory information undergoes a series of transformations as it travels from the olfactory epithelium to the olfactory bulb and then to the olfactory cortex.

The olfactory epithelium has a series of spatial zones that express different olfactory receptors. Each receptor type is expressed in approximately 5,000 neurons that are confined to one zone (Figure 29–5). (Recall that each neuron expresses only one odorant receptor gene.) Neurons with the same receptor are randomly scattered within a zone so neurons with different receptors are interspersed. All zones contain a variety of receptors, and a specific odorant may be recognized by receptors in different zones. Thus, despite a rough organization of odorant receptors into spatial

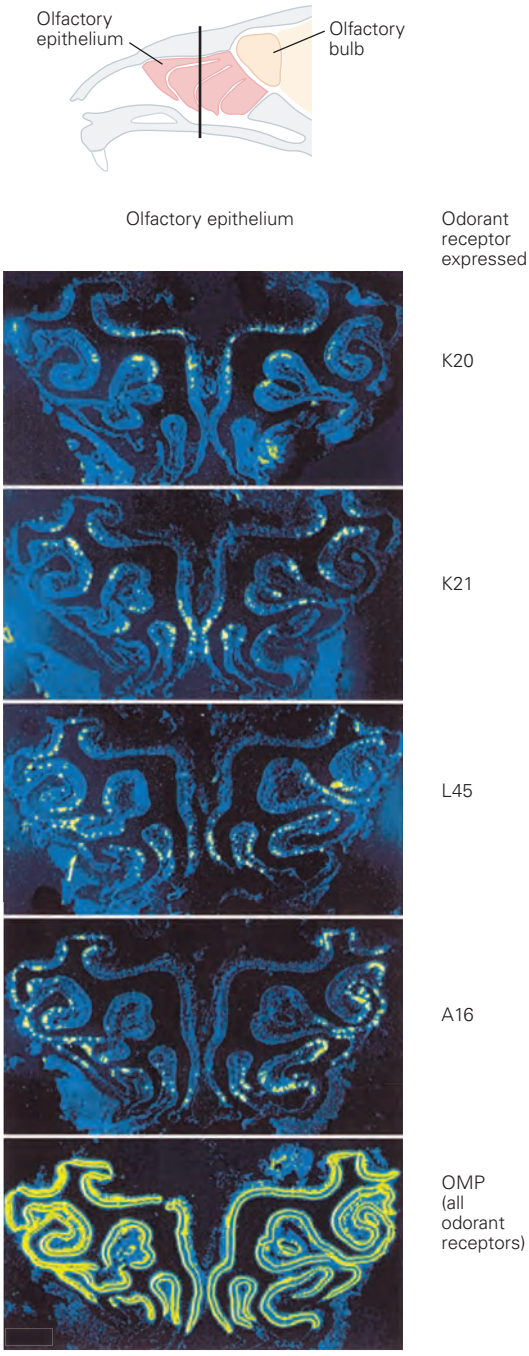

Figure 29–5 Organization of sensory inputs in the olfactory epithelium. The olfactory epithelium has different spatial zones that express different sets of odorant receptor genes. Each sensory neuron expresses only one receptor gene and thus one type of receptor. Neurons with the same receptor are confined to one zone but randomly scattered within that zone, such that neurons with different receptors are interspersed. The micrographs show the distribution of neurons labeled by four different receptor probes in sections through the mouse nose. An olfactory marker protein (OMP) probe labels all neurons expressing odorant receptors. (Adapted, with permission, from Ressler, Sullivan, and Buck 1993; Sullivan et al. 1996.)

zones, information provided by the odorant receptor family is highly distributed in the epithelium.

Because each odorant is detected by an ensemble of neurons widely dispersed across the epithelial sheet, receptors in one part of the epithelium will be able to detect a particular odorant even when those in another part are impaired by respiratory infection.

Sensory Inputs in the Olfactory Bulb Are Arranged by Receptor Type

The axons of olfactory sensory neurons project to the ipsilateral olfactory bulb, whose rostral end lies just above the olfactory epithelium. The axons of olfactory sensory neurons terminate on the dendrites of olfactory bulb neurons within bundles of neuropil called glomeruli that are arrayed over the bulb's surface (Figure 29–1). In each glomerulus, the sensory axons make synaptic connections with three types of neurons: mitral and tufted projection (relay) neurons, which project axons to the olfactory cortex, and periglomerular interneurons, which encircle the glomerulus (Figure 29–6).

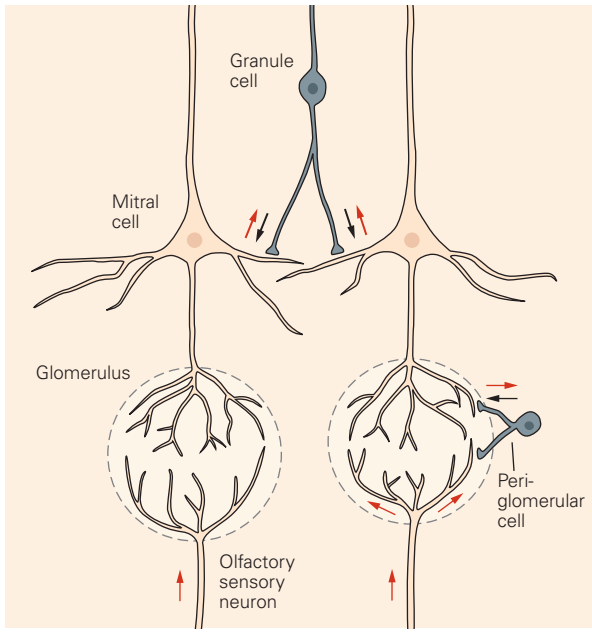

Figure 29–6 Olfactory bulb interneurons. In addition to excitatory mitral and tufted relay neurons, the olfactory bulb contains inhibitory interneurons. Within each glomerulus, the dendrites of GABAergic periglomerular cells receive excitatory input from olfactory sensory neurons and have reciprocal synapses with the primary dendrites of mitral and tufted relay neurons, suggesting a possible role in signal modification. The dendrites of GABAergic granule cells deeper in the bulb have reciprocal excitatory-inhibitory synapses with the secondary dendrites of the relay neurons and are thought to provide negative feedback to relay neurons that shapes the odor response. (Adapted from Shepherd and Greer 1998.)

The axon of an olfactory sensory neuron as well as the primary dendrite of each mitral and tufted relay neuron terminate in a single glomerulus. In each glomerulus, the axons of several thousand sensory neurons converge on the dendrites of approximately 40 to 50 relay neurons. This convergence results in approximately a 100-fold decrease in the number of neurons transmitting olfactory signals.

The organization of sensory information in the olfactory bulb is dramatically different from that of the epithelium. Whereas olfactory sensory neurons with the same odorant receptor are randomly scattered in one epithelial zone, their axons typically converge in two glomeruli at specific locations, one on either side of the olfactory bulb (Figure 29–7C). Each glomerulus, and each mitral and tufted relay neuron connected to it, receives input from just one type of odorant receptor. The result is a precise arrangement of sensory inputs from different odorant receptors, one that is similar between individuals.

Because each odorant is recognized by a unique combination of receptor types, each also activates a particular combination of glomeruli in the olfactory bulb (Figure 29–7B). At the same time, just as one odorant receptor recognizes multiple odorants, a single glomerulus—or a given mitral or tufted cell—is activated by more than one odorant. Owing to the nearly stereotyped pattern of receptor inputs in the olfactory bulb, the patterns of glomerular activation elicited by individual odorants are similar in all individuals and are bilaterally symmetrical in the two adjacent bulbs.

This organization of sensory information in the olfactory bulb is likely to be advantageous in two respects. First, signals from thousands of sensory neurons with the same odorant receptor type always converge on the same few glomeruli, and relay neurons in the olfactory bulb may optimize the detection of odorants present at low concentrations. Second, although olfactory sensory neurons with the same receptor type are dispersed and are continually replaced, the arrangement of inputs in the olfactory bulb remains unaltered. As a result, the neural code for an odorant in the brain is maintained over time, assuring that an odorant encountered previously can be recognized years later.

One mystery that remains unsolved is how all the axons of olfactory sensory neurons with the same type of receptor are directed to the same glomeruli. Studies using transgenic mice indicate that the odorant receptor itself somehow determines the target of the axon, but how it does so is not yet understood.

Sensory information is processed and possibly refined in the olfactory bulb before it is forwarded to the olfactory cortex. Each glomerulus is encircled by periglomerular interneurons that receive excitatory input from sensory axons and form inhibitory dendrodendritic synapses with mitral and tufted cell dendrites in that glomerulus and perhaps adjacent glomeruli. The periglomerular interneurons may therefore have a role in signal modulation. In addition, granule cell interneurons deep in the bulb provide negative feedback onto mitral and tufted cells. The granule cell interneurons are excited by the basal dendrites of mitral and tufted cells and in turn inhibit those relay neurons and others with which they are connected. The lateral inhibition afforded by these connections is thought to dampen signals from glomeruli and relay neurons that respond to an odorant only weakly, thereby sharpening the contrast between important and irrelevant sensory information before its transmission to the cortex.

Other potential sources of signal refinement are the retrograde projections to the olfactory bulb from the olfactory cortex, basal forebrain (horizontal limb of the diagonal band), and midbrain (locus ceruleus and raphe nuclei). These connections may modulate olfactory bulb output according to the physiological or behavioral state of an animal. When the animal is hungry, for example, some centrifugal projections might heighten the perception of the aroma of foods.

The Olfactory Bulb Transmits Information to the Olfactory Cortex

The axons of the mitral and tufted relay neurons of the olfactory bulb project through the lateral olfactory tract to the olfactory cortex (Figure 29–8 and see Figure 29–1). The olfactory cortex, defined roughly as that portion of the cortex that receives a direct projection from the olfactory bulb, comprises multiple anatomically distinct areas. The six major areas are the anterior olfactory nucleus, which connects the two olfactory bulbs through a portion of the anterior commissure; the anterior and posterior-lateral cortical nuclei of the amygdala; the olfactory tubercle; part of the entorhinal cortex; and the piriform cortex, the largest and considered the major olfactory cortical area.

The functions of the different olfactory cortical areas are largely unknown. However, the piriform cortex is thought to be important for odor learning. Recent studies indicate that the posterior-lateral cortical amygdala may have a role in innate attraction and fear behaviors, and the amygdalo-piriform transition area, a minor olfactory cortical area, a role in stress hormone responses to predator odors detected in the nose.

In the piriform cortex, the axons of olfactory bulb mitral and tufted cells leave the lateral olfactory tract

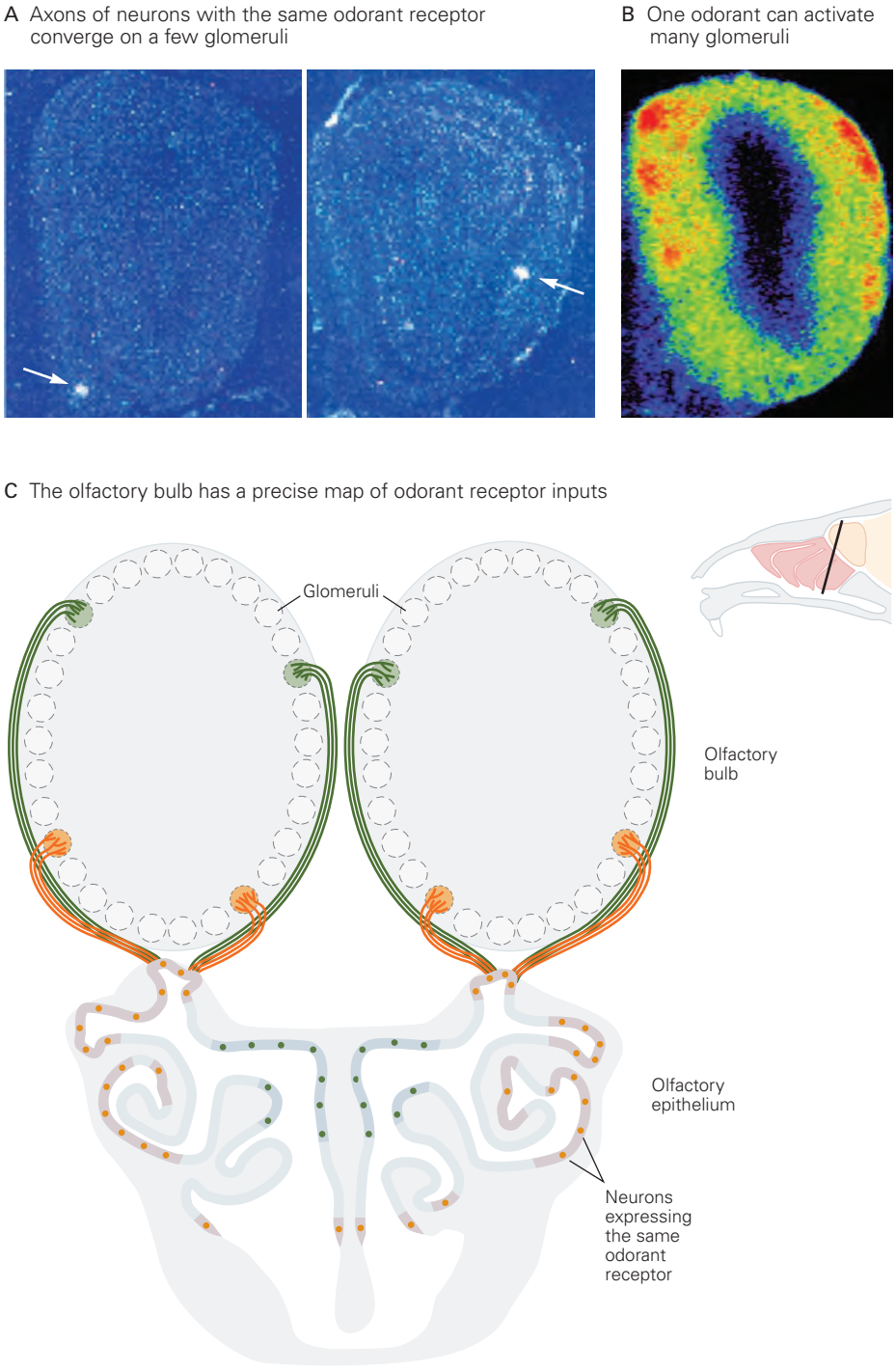

Figure 29–7 Odor responses in the olfactory bulb.

A. The axons of sensory neurons with the same odorant receptor type usually converge in only two glomeruli, one on each side of the olfactory bulb. Here, a probe specific for one odorant receptor gene labeled a glomerulus on the medial side (*left*) and lateral side (*right*) of a mouse olfactory bulb. The probe hybridized to receptor messenger RNAs present in sensory axons in these coronal sections. (Adapted, with permission, from Ressler, Sullivan, and Buck 1994.)

B. A single odorant often activates multiple glomeruli with input from different receptors. This section of a rat olfactory bulb shows the uptake of radiolabeled 2-deoxglucose at multiple foci (**red**) following exposure of the animal to the odorant methyl benzoate. The labeled foci correspond to numerous glomeruli at different locations in the olfactory bulb. (Reproduced, with permission, from Johnson, Farahbod, and Leon 2005. Copyright © 2005 Wiley-Liss, Inc.)

C. The olfactory bulb has a precise map of odorant receptor inputs because each glomerulus is dedicated to only one type of receptor. The maps in the two olfactory bulbs are bilaterally symmetrical and are nearly identical across individuals. The maps on the medial and lateral sides of each bulb are similar, but slightly displaced along the dorsal-ventral and anterior-posterior axes.

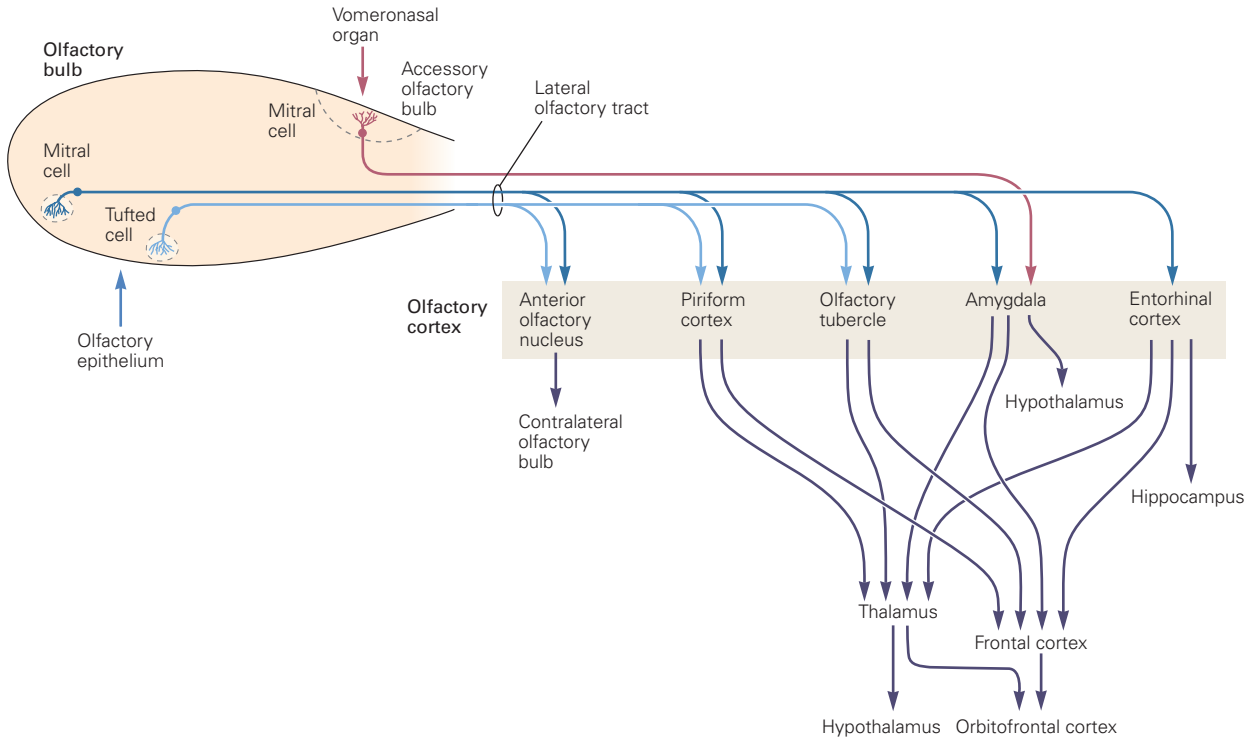

Figure 29–8 Afferent pathways to olfactory cortex. The axons of mitral and tufted relay neurons of the olfactory bulb project through the lateral olfactory tract to the olfactory cortex. The olfactory cortex consists of a number of distinct areas, the largest of which is the piriform cortex. From these areas, olfactory information is transmitted to other brain areas directly as well as indirectly via the thalamus. Targets include frontal and orbitofrontal areas of the neocortex, which are thought to be important for odor discrimination, and the amygdala and hypothalamus, which may be involved in emotional and physiological responses to odors. Mitral cells in the accessory olfactory bulb project to specific areas of the amygdala that transmit signals to the hypothalamus.

to form excitatory glutamatergic synapses with pyramidal neurons, the projection neurons of the cortex. Pyramidal neuron activity appears to be modulated by inhibitory inputs from local GABAergic interneurons as well as by excitatory inputs from other pyramidal neurons in the same and other olfactory cortical areas and the contralateral piriform cortex. The piriform cortex also receives centrifugal inputs from modulatory brain areas, suggesting that its activity may be adjusted according to physiological or behavioral state. Finally, the olfactory cortex projects to the olfactory bulb, providing yet another possible means of signal modulation.

As with the olfactory bulb relay neurons, individual pyramidal neurons can be activated by more than one odorant. However, the pyramidal neurons activated by a particular odorant are scattered across the piriform cortex, an arrangement different from that of the olfactory bulb. Mitral cells in different parts of the olfactory bulb can project axons to the same subregion of the piriform cortex, further indicating that the highly organized map of odorant receptor inputs in the olfactory bulb is not recapitulated in the cortex.

Output From the Olfactory Cortex Reaches Higher Cortical and Limbic Areas

Pyramidal neurons in the olfactory cortex transmit information indirectly to the orbitofrontal cortex through the thalamus and directly to the frontal cortex. These pathways to higher cortical areas are thought to be important in odor discrimination. In fact, people with lesions of the orbitofrontal cortex are unable to discriminate odors. Interestingly, recordings in the orbitofrontal cortex suggest that some individual neurons in that area receive multimodal input, responding, for example, to the smell, sight, or taste of a banana.

Many areas of the olfactory cortex also relay information to nonolfactory areas of the amygdala, which is linked to emotions, and to the hypothalamus, which controls basic drives, such as appetite, as well as a number of innate behaviors. These limbic areas are thought to play a role in the emotional and motivational aspects of smell as well as many of the behavioral and physiological effects of odorants. In animals, they may be important in the generation of

stereotyped behavioral and physiological responses to odors of predators or to pheromones that are detected in the olfactory epithelium.

Olfactory Acuity Varies in Humans

Olfactory acuity can vary as much as 1,000-fold among humans, even among people with no obvious abnormality. The most common olfactory aberration is *specific anosmia*. An individual with a specific anosmia has lowered sensitivity to a specific odorant even though sensitivity to other odorants appears normal. Specific anosmias to some odorants are common, with a few occurring in 1% to 20% of people. For example, 12% of individuals tested in one study exhibited a specific anosmia for musk. Recent studies indicate that specific anosmias can be caused by mutations in particular odorant receptor genes.

Far rarer abnormalities of olfaction, such as *general anosmia* (complete lack of olfactory sensation) or *hyposmia* (diminished sense of smell), are often transient and can derive from respiratory infections. Chronic anosmia or hyposmia can result from damage to the olfactory epithelium caused by infections; from particular diseases, such as Parkinson disease; or from head trauma that severs the olfactory nerves passing through holes in the cribriform plate, which then become blocked by scar tissue. Olfactory hallucinations of repugnant smells (*cacosmia*) can occur as a consequence of epileptic seizures.

Odors Elicit Characteristic Innate Behaviors

Pheromones Are Detected in Two Olfactory Structures

In many animals, the olfactory system detects not only odors but also pheromones, chemicals that are released from animals and influence the behavior or physiology of members of the same species. Pheromones play important roles in a variety of mammals, although they have not been demonstrated in humans. Often contained in urine or glandular secretions, some pheromones modulate the levels of reproductive hormones or stimulate sexual behavior or aggression. Pheromones are detected by two separate structures: the nasal olfactory epithelium, where odorants are detected, and the vomeronasal organ, an accessory olfactory organ thought to be specialized for the detection of pheromones and other animal cues.

The vomeronasal organ is present in many mammals, although not in humans. It is a tubular structure in the nasal septum that has a duct opening into the nasal cavity and one inner wall lined by a sensory epithelium. Signals generated by sensory neurons in the epithelium of the vomeronasal organ follow a distinct pathway. They travel through the accessory olfactory bulb primarily to the medial amygdala and posterior-medial cortical amygdala and from there to the hypothalamus.

Sensory detection in the vomeronasal organ differs from that in the olfactory epithelium. The vomeronasal organ has two different families of chemosensory receptors, the V1R and V2R families. In the mouse, each family has more than 100 members. Variation in amino acid sequence between members of each receptor family suggests that each family may recognize a variety of different ligands. Like odorant receptors, V1R and V2R receptors have the seven transmembrane domains typical of G protein–coupled receptors. The V2R receptor differs from both V1R and odorant receptors in having a large extracellular domain at the N-terminal end (Figure 29–9A). By analogy with receptors with similar structures, ligands may bind V1R receptors in a membrane pocket formed by a combination of transmembrane domains, whereas binding to V2R receptors may occur in the large extracellular domain. Although the V1R receptors are thought to recognize volatile chemicals, at least some V2Rs are thought to recognize proteins. These include a protein pheromone present in tears, mouse urinary proteins that stimulate aggression, and predator proteins from cats and rats that stimulate fear in mice.

The V1R and V2R families are expressed in different spatial zones in the vomeronasal organ that express different G proteins (Figure 29–9B,C). Each *V1R* or *V2R* gene is expressed in a small percentage of neurons scattered throughout one zone, an arrangement similar to that of odorant receptors in the olfactory epithelium. Similar to the main olfactory bulb, vomeronasal neurons with the same receptor type project to the same glomeruli in the accessory olfactory bulb, although the glomeruli for each receptor type are more numerous and their distribution less stereotyped than in the main olfactory bulb. In addition to V1R and V2R receptors, the vomeronasal organ has a family of five formyl peptide-related receptors (FPRs). These receptors are related to immune system FPRs that detect bacterial proteins, raising speculation that they might play a role in detecting diseased animals of the same species.

Invertebrate Olfactory Systems Can Be Used to Study Odor Coding and Behavior

Because invertebrates have simple nervous systems and often respond to olfactory stimuli with stereotyped

behaviors, they are useful for understanding the relationship between the neural representation of odor and behavior.

Certain features of chemosensory systems are highly conserved in evolution. First, all metazoan animals can detect a variety of organic molecules using specialized chemosensory neurons with cilia or microvilli that contact the external environment. Second, the initial events of odor detection are mediated by families of transmembrane receptors with specific expression patterns in peripheral sensory neurons. Other features of the olfactory system differ between species, reflecting selection pressures and evolutionary histories of the animals.

The primary sensory organs of insects are the antennae and appendages known as maxillary palps near the mouth (Figure 29–10A). Whereas mammals have millions of olfactory neurons, insects have a much smaller number. There are approximately 2,600 olfactory neurons in the fruit fly *Drosophila* and approximately 60,000 in the honeybee.

The insect odorant receptors were discovered by finding multigene receptor families in the *Drosophila* genome, and these genes have now been examined in other insect genomes as well. Remarkably, they have little similarity to mammalian odorant receptors save for the presence of many transmembrane domains. Indeed, insect receptors appear to have an independent evolutionary origin from mammalian receptors and may not even be G protein–coupled receptors—an extreme example of the fast evolutionary change observed across all olfactory receptor systems. In *Drosophila*, the main odorant receptor family has only 60 genes, rather than the hundreds characteristic of vertebrates. The malaria mosquito *Anopheles gambiae* and the honeybee have similar numbers (85–95 genes), whereas leaf-cutter ants have more than 350 odorant

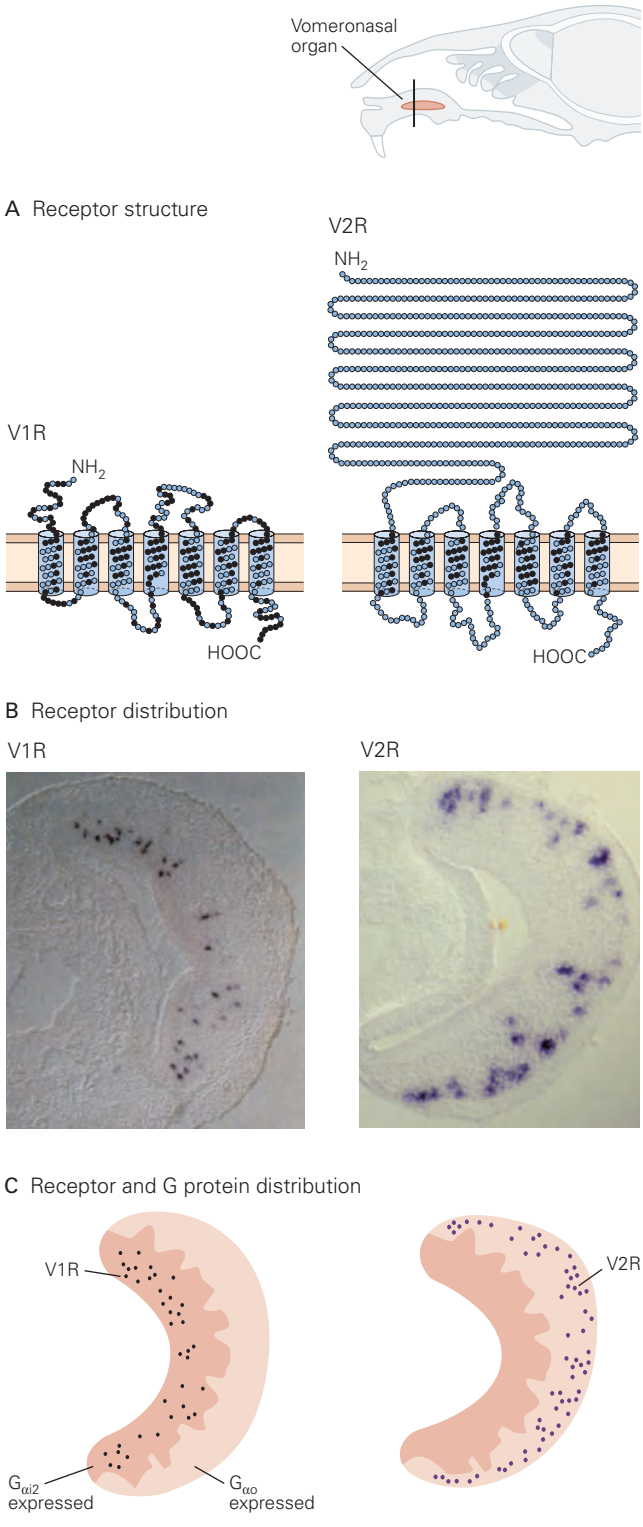

Figure 29–9 (Right) Candidate pheromone receptors in the vomeronasal organ.

A. The V1R and V2R families of receptors are expressed in the vomeronasal organ. In the mouse, each family has more than 100 members, which vary in protein sequence. Members of both families have the seven transmembrane domains of G protein–coupled receptors, but V2R receptors also have a large extracellular domain at the N-terminal end that may be the site of ligand binding.

B. Sections through the vomeronasal organ show individual V1R and V2R probes hybridized to subsets of neurons in two distinct zones. (Reproduced, with permission, from Dulac and Axel 1995; Matsunami and Buck 1997.)

C. The two zones express high levels of different G proteins, $G\alpha_{\alpha i2}$ and $G\alpha_{\alpha o}$.