Chapter 29: Smell and Taste: The Chemical Senses

Introduction

THROUGH THE SENSES OF SMELL and taste, we are able to perceive a staggering number and variety of chemicals in the external world. These chemical senses inform us about the availability of foods and their potential pleasure or danger. Smell and taste also initiate physiological changes required for the digestion and utilization of food. In many animals, the olfactory system also serves an important social function by detecting pheromones that elicit innate behavioral or physiological responses.

Although the discriminatory ability of humans is somewhat limited compared with that of many other animals, odor chemists estimate that the human olfactory system may be capable of detecting more than 10,000 different volatile chemicals. Perfumers who are highly trained to discriminate odorants can distinguish as many as 5,000 different types of odorants, and wine tasters can discern more than 100 different components of taste based on combinations of flavor and aroma.

In this chapter, we consider how odor and taste stimuli are detected and how they are encoded in patterns of neural signals transmitted to the brain. In recent years, much has been learned about the mechanisms underlying chemosensation in a variety of animal species. Certain features of chemosensation have been conserved through evolution, whereas others are specialized adaptations of individual species.

A Large Family of Olfactory Receptors Initiate the Sense of Smell

Odorants—volatile chemicals that are perceived as odors—are detected by olfactory sensory neurons in the nose. The sensory neurons are embedded in a specialized olfactory epithelium that lines part of the nasal cavity, approximately 5 cm^2 in area in humans (Figure 29–1), and are interspersed with glia-like supporting cells (Figure 29–2). They are relatively short lived, with a life span of only 30 to 60 days, and are continuously replaced from a layer of basal stem cells in the epithelium.

Figure 29–1

The olfactory system. Odorants are detected by olfactory sensory neurons in the olfactory epithelium, which lines part of the nasal cavity. The axons of these neurons project to the olfactory bulb, where they terminate on the dendrites of mitral and tufted cell relay neurons within glomeruli. In turn, the axons of the relay neurons project to the olfactory cortex, where they terminate on the dendrites of pyramidal neurons whose axons project to other brain areas.

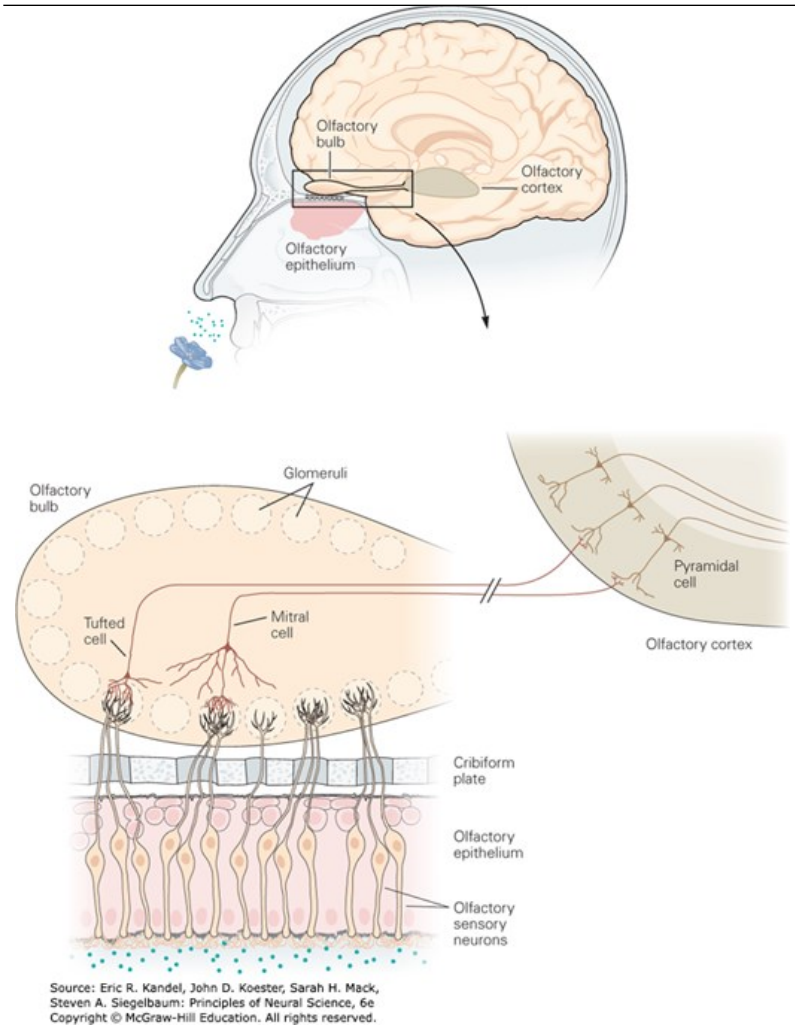
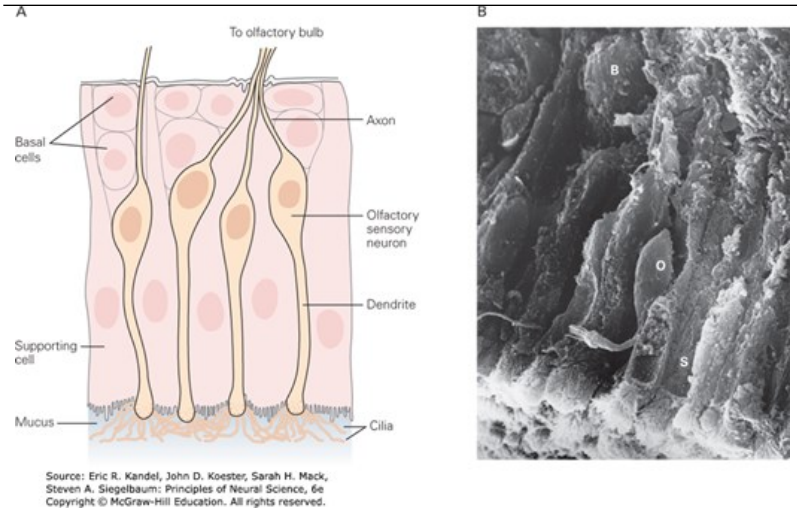


Figure 29–2

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.)



The olfactory sensory neuron is a bipolar nerve cell. A single dendrite extends from the apical end to the epithelial surface, where it gives rise to numerous 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

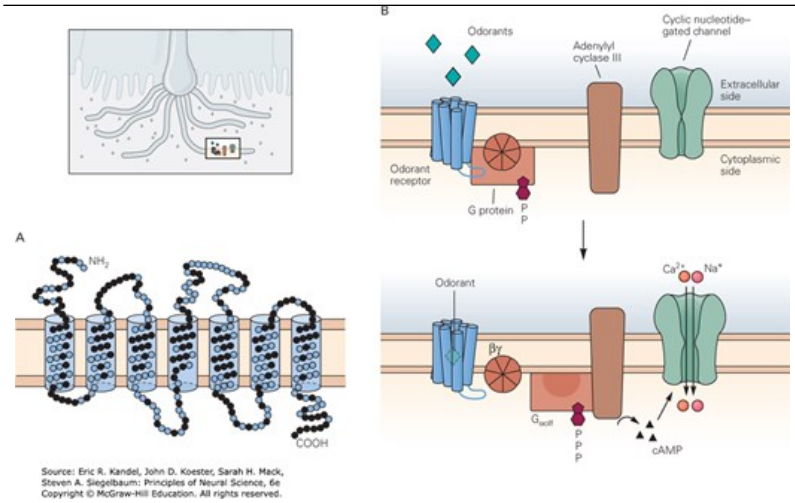
Odorant receptors are proteins encoded by a multigene family that is evolutionarily conserved and found in all vertebrate species. Humans have approximately 350 different odorant receptors, whereas mice have approximately 1,000. Although odorant receptors belong to the G protein–coupled receptor superfamily,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

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.



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 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.

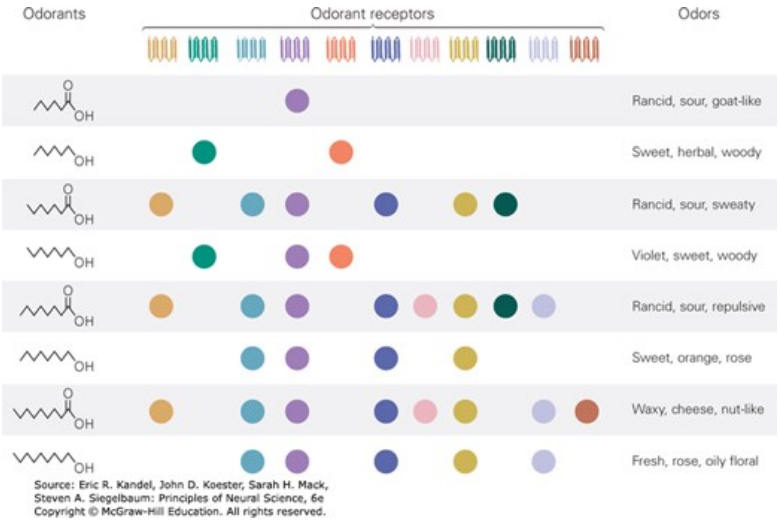
Different Combinations of Receptors Encode Different Odorants

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.

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.

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.)



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

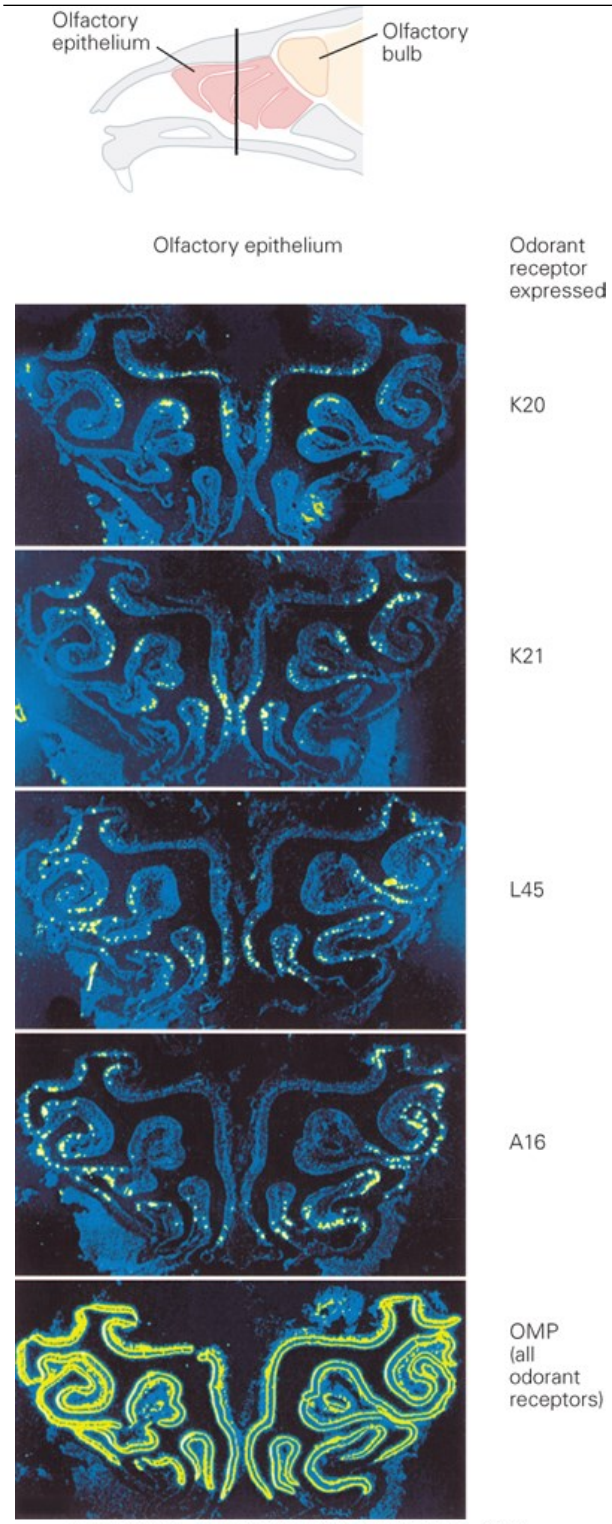
Odorants Are Encoded in the Nose by Dispersed Neurons

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

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.)



Source: Eric R. Kandel, John D. Koester, Sarah H. Mack, Steven A. Siegelbaum: Principles of Neural Science, 6e

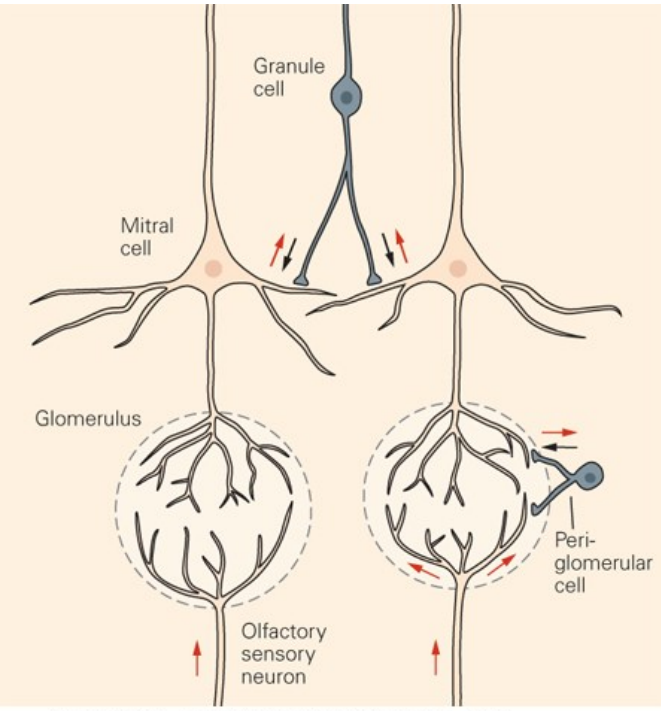
Because each odorant is detected by an ensemble of neurons widely dispersed across the epithelial sheet, receptors in one part of the epithelium will be able to detect a particular odorant even when those in another part are impaired by respiratory infection.

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.

Figure 29–7

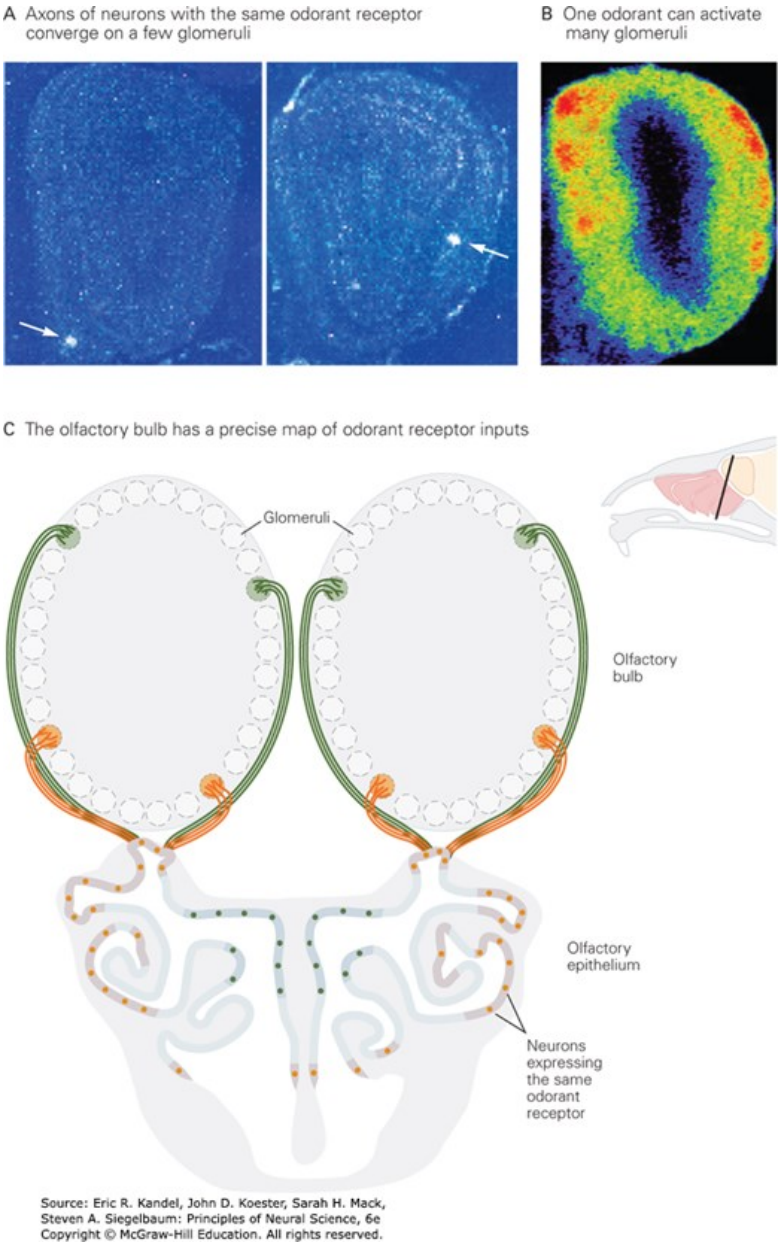
Odor responses in the olfactory bulb.

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.



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.

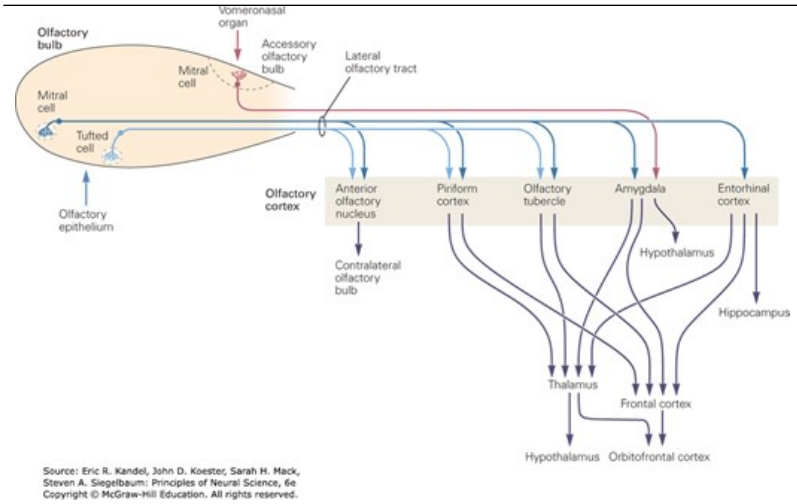
Other potential sources of signal refinement are the retrograde projections to the olfactory bulb from the olfactory cortex, basal forebrain (horizontal limb of the diagonal band), and midbrain (locus ceruleus and raphe nuclei). These connections may modulate olfactory bulb output according to the physiological 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.

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.



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 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.

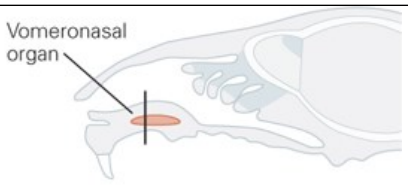
Figure 29–9

(Right) Candidate pheromone receptors in the vomeronasal organ.

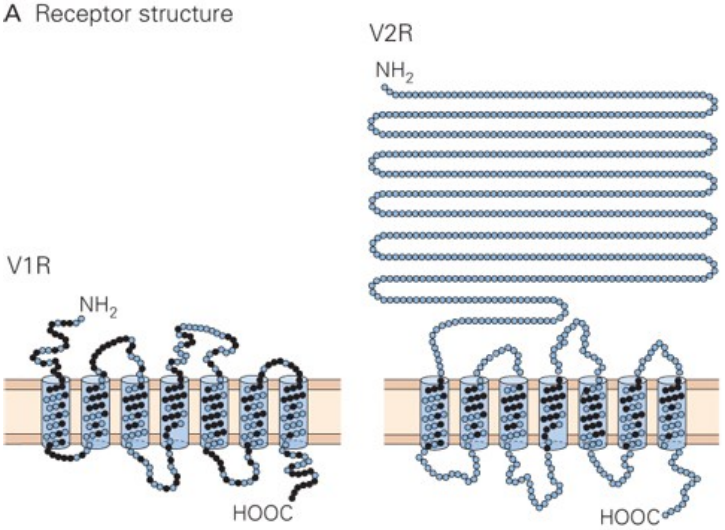
A. The V1R and V2R families of receptors are expressed in the vomeronasal organ. In the mouse, each family has more than 100 members, which vary in protein sequence. Members of both families have the seven transmembrane domains of G protein–coupled receptors, but V2R receptors also have a large extracellular 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.)

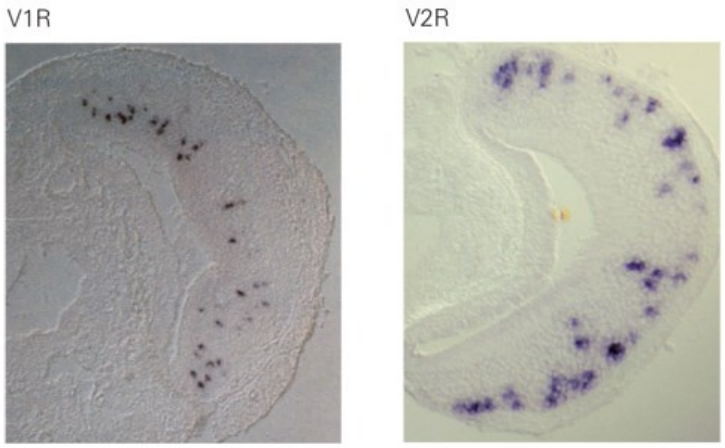
C. The two zones express high levels of different G proteins, $G\alpha_{\alpha i2}$ and $G\alpha_{\alpha o}$.



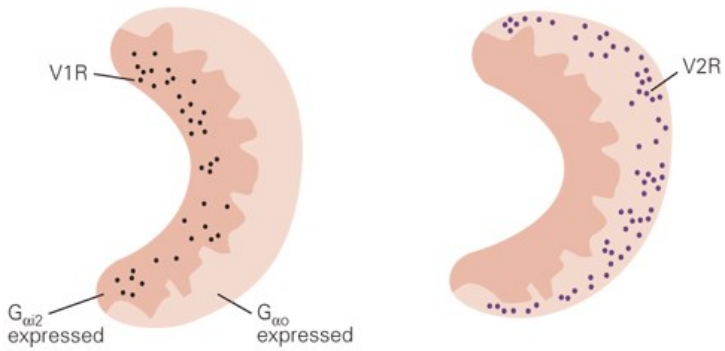
A Receptor structure



B Receptor distribution



C Receptor and G protein distribution



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.

Figure 29–10

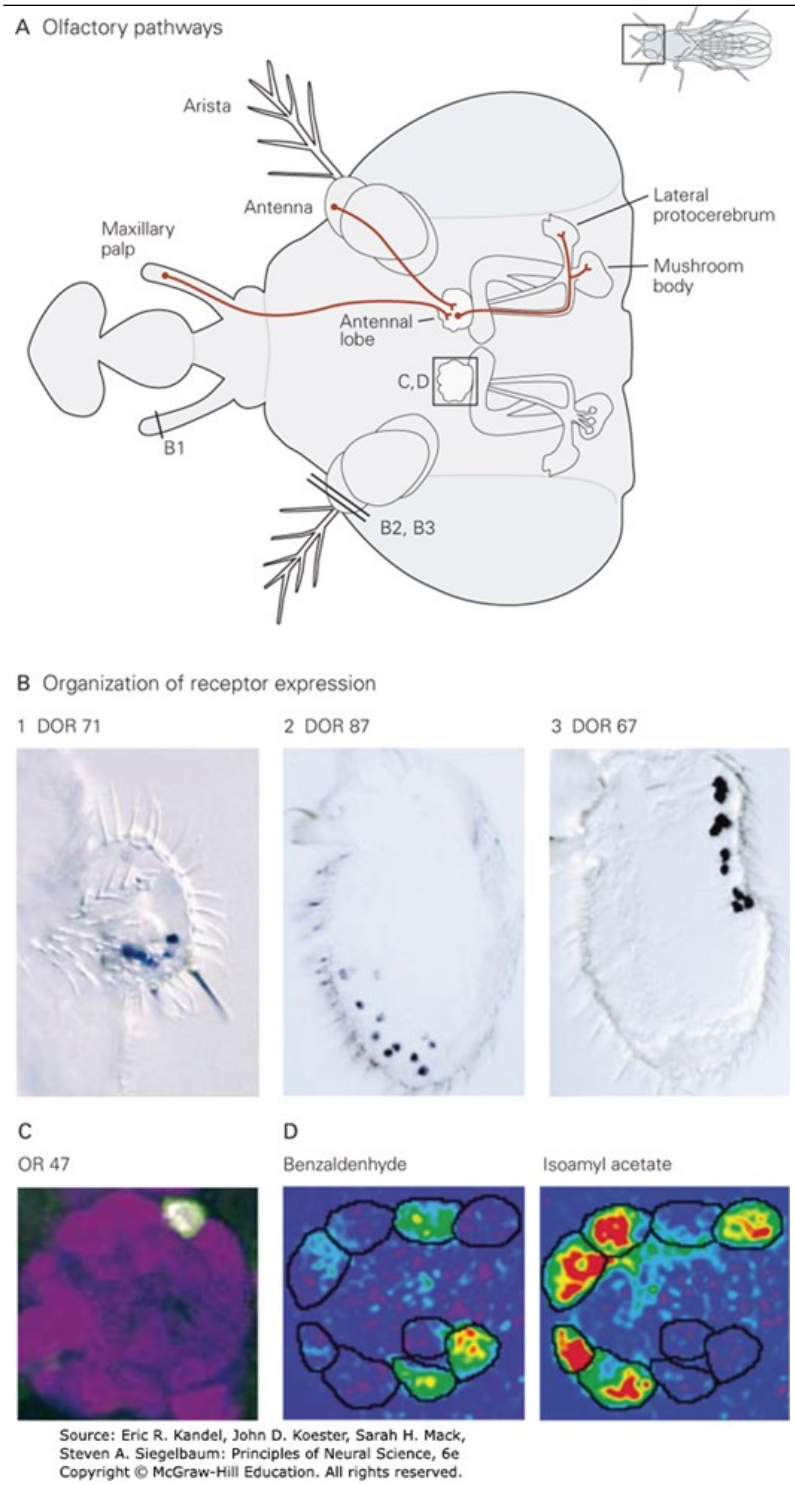
Olfactory pathways from the antenna to the brain in *Drosophila*.

A. The axons of olfactory neurons with cell bodies and dendrites in the antenna and maxillary palp project axons to the antennal lobe. Projection neurons in the antennal lobe then project to two regions of the fly brain, the mushroom body and lateral protocerebrum. (Reproduced, with permission, from Takaki Komiyama and Liqun Luo.)

B. The neurons that express one type of olfactory receptor gene, detected by RNA in situ hybridization, are scattered in the maxillary palp (**1**) or antenna (**2**, **3**).

C. All neurons that express the olfactory receptor gene *OR47* converge on a glomerulus in the antennal lobe. (Reproduced, with permission, from Vosshall et al. 1999; Vosshall, Wong, and Axel 2000.)

D. Each odorant elicits a physiological response from a subset of glomeruli in the antennal lobe. Two-photon calcium imaging was used to detect odor-evoked signals. (Reproduced, with permission, from Wang et al. 2003. Copyright © 2003 Elsevier.)



Source: Eric R. Kandel, John D. Koester, Sarah H. Mack, Steven A. Siegelbaum: Principles of Neural Science, 6e

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 receptor genes, suggesting a wide variation in receptor number in insects.

Despite molecular differences in receptors, the anatomical organization of the fly's olfactory system is quite similar to that of vertebrates. Each olfactory neuron expresses one or sometimes two functional odorant receptor genes. The neurons expressing a particular gene are loosely localized to a region of the antenna but interspersed with neurons expressing other genes (Figure 29–10B). This scattered distribution is not the case at the next level of organization, the antennal lobe. Axons from sensory neurons that express one type of receptor converge on two invariant glomeruli in the antennal lobe, one each on the left and right sides of the animal (Figure 29–10C). This organization is strikingly similar to that of the first sensory relay in the vertebrate olfactory bulb and is also found in the moth, honeybee, and other insects.

Because there are only a few dozen receptor genes in *Drosophila*, it is possible to characterize the entire repertory of odorant-receptor interactions, a goal that is not yet attainable in mammals. Sophisticated genetic methods can be used to label and record from a *Drosophila* neuron expressing a single known odorant receptor gene. By repeating this experiment with many receptors and odors, the receptive fields of the odorant receptors have been defined and shown to be quite diverse.

In insects, individual odorant receptors can detect large numbers of odorants, including odorants with very different chemical structures. This broad recognition of odorants by "generalist" receptors is necessary if only a small number of receptors is available to detect all biologically significant odorants. A single insect receptor protein that detects many odors can be stimulated by some odors and inhibited by others, often with distinct temporal patterns. A subset of insect odorant receptors that convey information about pheromones or other unusual odors like carbon dioxide are more selective. Thus, the coding potential of each olfactory neuron can be broad or narrow and arises from a combination of stimulatory and inhibitory signals delivered to its receptors.

Information from the olfactory neurons is relayed to the antennal lobe where sensory neurons expressing the same odorant receptor converge onto a small number of projection neurons in one glomerulus (Figure 29–10A). Because *Drosophila* glomeruli are stereotyped in position and have one type of odorant receptor input, the transformation of information across the synapse can be described. Convergence of many olfactory sensory axons onto a few projection neurons leads to a great increase in the signal-to-noise ratio of olfactory signals, so projection neurons are much more sensitive to odor than individual olfactory neurons. Within the antennal lobe, excitatory interneurons distribute signals to projection neurons at distal locations, and inhibitory interneurons feed back onto the olfactory sensory neurons to dampen their input. Thus, while activity of an individual olfactory neuron is conveyed to one glomerulus. its activity is also distributed across the entire antennal lobe, as it is processed by excitatory and inhibitory local interneurons that connect many glomeruli.

The projection neurons from the antennal lobe extend to higher brain centers called mushroom bodies and lateral protocerebrum (Figure 29–10A). These structures may represent insect equivalents of the olfactory cortex. The mushroom bodies are sites of olfactory associative learning and multimodal associative learning; the lateral protocerebrum is important for innate olfactory responses. At this stage, projection neurons form complex connections with a large number of downstream neurons. Neurons in higher brain centers in *Drosophila* have the potential to integrate information from many receptors.

Olfactory Cues Elicit Stereotyped Behaviors and Physiological Responses in the Nematode

The nematode roundworm *Caenorhabditis elegans* has one of the simplest nervous systems in the animal kingdom, with only 302 neurons in the entire animal. Of these, 32 are ciliated chemosensory neurons. Because *C. elegans* has strong behavioral responses to a wide variety of chemicals, it has been a useful experimental animal for relating olfactory signals to behavior. Each chemosensory neuron detects a specific set of chemicals, and activation of the neuron is required for the behavioral responses to those substances. The neuron for a particular response, such as attraction to a specific odor, occurs in the same position in all individuals.

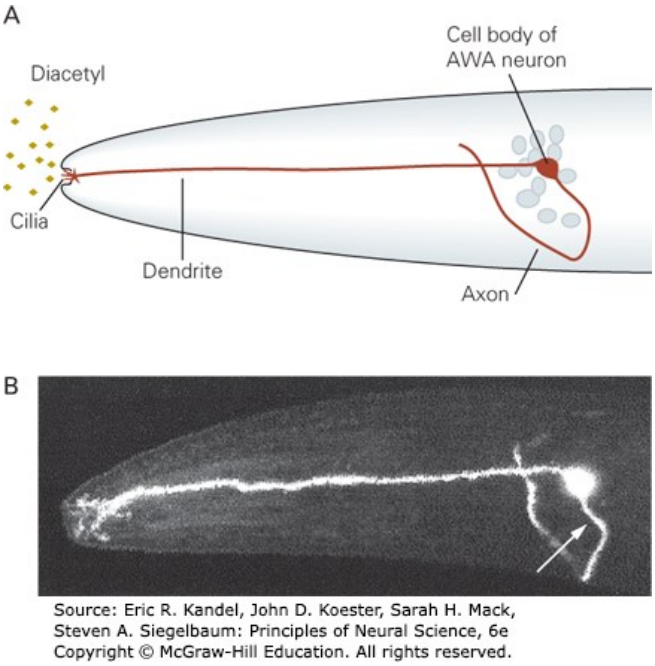
The molecular mechanisms of olfaction in *C. elegans* were elucidated through genetic screens for mutant worms lacking the ability to detect odors (anosmia). The G protein–coupled receptor for the volatile odorant diacetyl emerged from these screens (Figure 29–11). This receptor is one of approximately 1,700 predicted G protein–coupled chemoreceptor genes in *C. elegans*, the largest number of chemoreceptors among known genomes. Other kinds of chemosensory receptors are also present; for example, *C. elegans* senses external oxygen levels indirectly by detecting soluble guanylate cyclases that bind directly to oxygen. With so many chemoreceptors, nematodes are able to recognize a large variety of odors with great sensitivity. Some chemosensory neurons use G proteins to regulate cyclic guanosine 3′,5′-monophosphate (cGMP) and a cGMP-gated channel, a signal transduction pathway like that of vertebrate photoreceptors. Other chemosensory neurons signal through a transient receptor potential vanilloid (TRPV) channel, like vertebrate nociceptive neurons.

Figure 29–11

The receptor for diacetyl in the *Caenorhabditis elegans* worm.

A. A lateral view of the worm's anterior end shows the cell body and processes of the AWA chemosensory neuron. A dendrite terminates in cilia that are exposed to environmental chemicals. The neuron detects the volatile chemical diacetyl; animals with a mutation in the *odr-10* gene are unable to sense diacetyl.

B. The *odr-10* gene is active only in the AWA neurons. The micrograph here shows the gene product marked with fusion to a fluorescent reporter protein; the **arrow** indicates the neuron's axon. (Reproduced, with permission, from Sarafi-Reinach and Sengupta 2000.)



The "one neuron, one receptor" principle observed in vertebrates and insects does not operate in nematodes because the number of neurons is much smaller than the number of receptors. Each chemoreceptor gene is typically expressed in only one pair of chemosensory neurons, but each neuron expresses many receptor genes. The small size of the *C. elegans* nervous system limits olfactory computations. For example, a single neuron responds to many odors, but odors can be distinguished efficiently only if they are sensed by different primary sensory neurons.

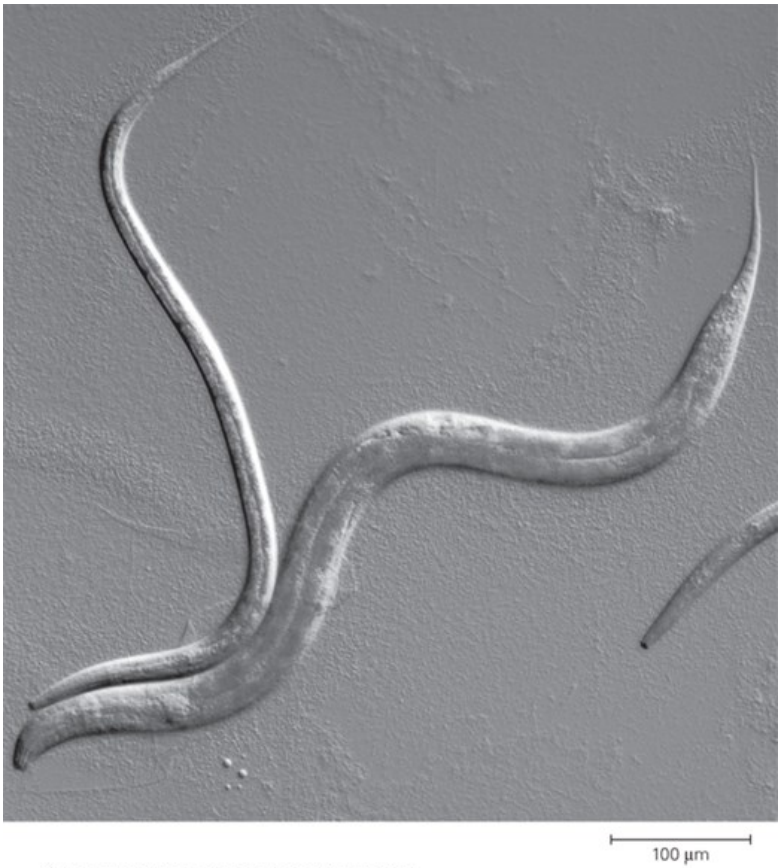
The relationship between odor detection and behavior has been explored in *C. elegans* through genetic manipulations. For example, diacetyl is normally attractive to worms, but when the diacetyl receptor is experimentally expressed in an olfactory neuron that normally senses repellents, the animals are instead repelled by diacetyl. This observation indicates that specific sensory neurons encode the hardwired behavioral responses of attraction or repulsion and that a "labeled line" connects specific odors to specific behaviors. Similar ideas have emerged from genetic manipulations of taste systems in mice and flies, where sweet and bitter preference pathways are encoded by different sets of sensory cells.

Olfactory cues are linked to physiological responses as well as behavioral responses in nematodes. Food and pheromone cues that regulate development are detected by specific sensory neurons through G protein–coupled receptors. With low pheromone levels and plentiful food, animals rapidly develop to adulthood, whereas with high pheromone levels and scarce food, animals arrest in a long-lived larval stage called *dauer larvae* (Figure 29–12). Activation of these sensory neurons ultimately regulates the activity of an insulin signaling pathway that controls physiology and growth as well as the life span of the nematode. It is an open question whether the chemosensory systems and physiological systems of other animals are as entangled as they are in nematodes.

Figure 29–12

Chemosensory cues regulate the development of *C. elegans*. When exposed to different chemosensory cues, two larvae of the same age follow different development paths. A dauer larva, which forms under stressful conditions of low food and high population density, develops into a small slender adult (*left*). It is a nonfeeding, nonreproducing, stress-resistant form of the worm. In contrast, a larva in a rich environment favoring

reproductive growth develops into a normal adult (*right*). (Reproduced, with permission, from Manuel Zimmer.)



Strategies for Olfaction Have Evolved Rapidly

Why have independent families of odorant receptors evolved in mammals, nematodes, and insects? And why have the families changed so rapidly compared to genes involved in other important biological processes? The answer lies in a fundamental difference between olfaction and other senses such as vision, touch, and hearing.

Most senses are designed to detect physical entities with reliable physical properties: photons, pressure, or sound waves. By contrast, olfactory systems are designed to detect organic molecules that are infinitely variable and do not fit into a simple continuum of properties. Moreover, the organic molecules that are detected are produced by other living organisms, which evolve far more rapidly than the world of light, pressure, and sound.

An ancient olfactory system was present in the common ancestor of all animals that exist today. That ancestor lived in the ocean, where it gave rise to different lineages for mammals, insects, and nematodes. Those three phyla of animals came onto land hundreds of millions of years after the phyla diverged. Each phylum independently modified its olfactory system to detect airborne odors, leading to diversification of the receptors.

A consideration of the natural history of dipteran and hymenopteran insects, which have evolved in the last 200 million years, helps explain the rapid diversification of the odorant receptors. These insects include honeybees that pollinate flowers, fruit flies that feed on rotting fruit, flesh flies that arrive within minutes of death, and mosquitoes that prey on living animals. The odorants important for the survival of these insects are radically different, and receptor genes tuned to those odorants have evolved accordingly.

The Gustatory System Controls the Sense of Taste

Taste Has Five Submodalities That Reflect Essential Dietary Requirements

The gustatory system is a specialized chemosensory system dedicated to evaluating potential food sources. It is the only sensory system that detects sugars and harmful compounds present in foods, and it serves as a main driver of feeding decisions. Unlike the olfactory system, which distinguishes millions of odors, the gustatory system recognizes just a few taste categories.

Humans and other mammals can distinguish five basic taste qualities: sweet, bitter, salty, sour, and umami, a Japanese word meaning delicious and associated with the “savory” taste of amino acids. This limited palate detects all essential dietary requirements of animals: A sweet taste invites consumption of energy-rich foods; bitter taste warns against the ingestion of toxic, noxious chemicals; salty taste promotes a diet that maintains proper electrolyte balance; sour taste signals acidic, unripened, or fermented foods; and umami indicates protein-rich foods.

Consistent with the nutritional importance of carbohydrates and proteins, both sweet and umami tastants elicit innately pleasurable sensations in humans and are attractants for animals in general. In contrast, bitter and sour tastants elicit innately aversive responses in humans and animals.

Taste is often thought to be synonymous with flavor. However, taste refers strictly to the five qualities encoded in the gustatory system, whereas flavor, with its rich and varied qualities, stems from the multisensory integration of inputs from the gustatory, olfactory, and somatosensory systems (eg, texture and temperature).

Tastant Detection Occurs in Taste Buds

Tastants are detected by taste receptor cells clustered in taste buds. Although the majority of taste buds in humans are located on the tongue surface, some can also be found on the palate, pharynx, epiglottis, and upper third of the esophagus.

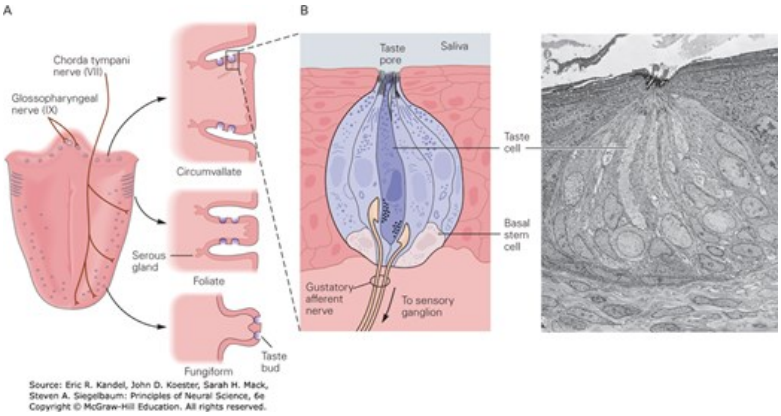
Taste buds on the tongue occur in structures called papillae, of which there are three types based on morphology and location. *Fungiform papillae*, located on the anterior two-thirds of the tongue, are peg-like structures that are topped with taste buds. Both the *foliate papillae*, situated on the posterior edge of the tongue, and the *circumvallate papillae*, of which there are only a few in the posterior area of the tongue, are structures surrounded by grooves lined with taste buds (Figure 29–13A). In humans, each fungiform papilla contains one to five taste buds, whereas each foliate and circumvallate papilla may contain hundreds to thousands of taste buds, respectively.

Figure 29–13

Taste buds are clustered in papillae on the tongue.

A. The three types of papillae—circumvallate, foliate, and fungiform—differ in morphology and location on the tongue and are differentially innervated by the chorda tympani and glossopharyngeal nerves.

B. Each taste bud contains 50 to 150 elongated taste receptor cells, as well as supporting cells and a small population of basal stem cells. The taste cell extends microvilli into the taste pore, allowing it to detect tastants dissolved in saliva. At its basal end, the taste cell contacts gustatory sensory neurons that transmit stimulus signals to the brain. The scanning electron micrograph shows a taste bud in a foliate papilla in a rabbit. (Reproduced, with permission, from Royer and Kinnamon 1991. Copyright © 1991 Wiley-Liss, Inc.)



The taste bud is a garlic-shaped structure embedded in the epithelium. A small opening at the epithelial surface, the taste pore, is the point of contact with tastants (Figure 29–13B). Each taste bud contains approximately 100 taste receptor cells (taste cells), elongated cells that stretch from the taste pore to the basal area of the bud. The taste bud also contains other elongated cells that are thought to serve a supporting function, as well as a small number of round cells at the base, which are thought to serve as stem cells. Each taste cell extends microvilli into the taste pore, allowing the cell to contact chemicals dissolved in saliva at the epithelial surface.

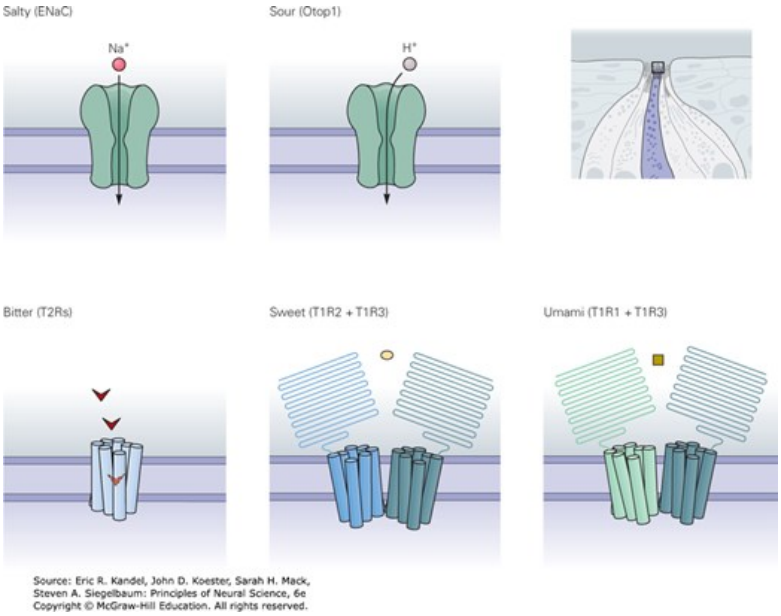
At its basal end, the taste cell contacts the afferent fibers of gustatory sensory neurons, whose cell bodies reside in specific sensory ganglia (see Figure 29–17). Although taste cells are nonneural, their contacts with the gustatory sensory neurons have the morphological characteristics of chemical synapses, including clustered presynaptic vesicles. Taste cells also resemble neurons in that they are electrically excitable; they have voltage-gated Na^+, K^+, and Ca^{2+} channels and are capable of generating action potentials. Taste cells are very short-lived (days to weeks) and are continually replaced from the stem cell population. This turnover requires that newborn taste cells differentiate to detect one of the five taste qualities and connect to the terminals of appropriate gustatory sensory neurons, such that a sweet taste cell connects to sweet sensory neurons and a bitter taste cell to bitter sensory neurons.

Each Taste Modality Is Detected by Distinct Sensory Receptors and Cells

The five taste qualities are detected by sensory receptors in the microvilli of different taste cells. There are two general types of receptors: Bitter, sweet, and umami tastants interact with G protein–coupled receptors, whereas salty and sour tastants interact directly with specific ion channels (Figure 29–14). These interactions depolarize the taste cell, leading to the generation of action potentials in the afferent gustatory fibers.

Figure 29–14

Sensory transduction in taste cells. Different taste qualities involve different detection mechanisms in the apical microvilli of taste cells (see Figure 29–13B). Salty and sour tastants directly activate ion channels, whereas tastants perceived as bitter, sweet, or umami activate G protein–coupled receptors. Bitter tastants are detected by T2R receptors, whereas sweet tastants are detected by a combination of T1R2 and T1R3, and umami tastants by a combination of T1R1 and T1R3.



Sweet Taste Receptor

Compounds that humans perceive as sweet include sugars, artificial sweeteners such as saccharin and aspartame, a few proteins such as monellin and thaumatin, and several D-amino acids. All of these sweet-tasting compounds are detected by a heteromeric receptor composed of two members of the T1R taste receptor family, T1R2 and T1R3 (Figure 29–15). The T1R receptors are a small family of three related G protein–coupled receptors that participate in sweet and umami detection.

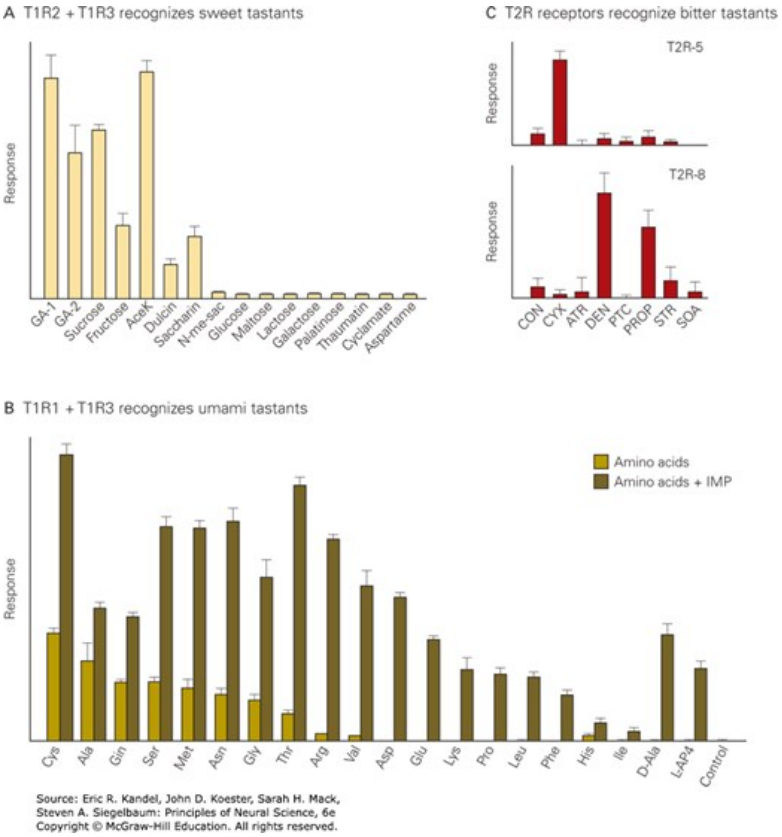
Figure 29–15

Tastants recognized by T1R and T2R receptors. A calcium-sensitive dye was used to test whether T1R and T2R receptors expressed in a tissue culture cell line could detect tastants.

A. Cells expressing both rat T1R2 and rat T1R3 responded to a number of sweet compounds. (Reproduced, with permission, from Nelson et al. 2001.)

B. Cells expressing mouse T1R1 and mouse T1R3 responded to numerous L-amino acids (umami taste). Responses were potentiated by inosine monophosphate (**IMP**). (Reproduced, with permission, from Nelson et al. 2002. Copyright © 2002 Springer Nature.)

C. Cells expressing different T2R receptors responded selectively to different bitter compounds. Cells expressing mouse T2R5 responded most vigorously to cycloheximide (**CYX**), whereas cells expressing mouse T2R8 responded preferentially to denatonium (**DEN**) and 6-n-propyl-2-thiouracil (**PROP**). (**ATR**, atropine; **CON**, control; **PTC**, phenyl thiocarbamide; **SOA**, sucrose octaacetate; **STR**, strychnine.) (Reproduced, with permission, from Chandrashekar et al. 2000.)



Receptors of the TIR family have a large N-terminal extracellular domain (Figure 29–14) that serves as the main ligand-binding domain, similar to the V2R receptor of vomeronasal neurons. This domain recognizes many different sugars with low-affinity binding in the millimolar range. This ensures that only high sugar concentrations of nutritive value are detected. Changing a single amino acid in this domain in mice can alter an animal's sensitivity to sweet compounds. Indeed, T1R3 was initially discovered by examining genes at the mouse saccharin preference (Sac) locus, a chromosomal region that governs sensitivity to saccharin, sucrose, and other sweet compounds.

In mice, taste cells with T1R2 receptors are found mostly in palate, foliate, and circumvallate papillae; almost invariably, those cells also possess T1R3 receptors (Figure 29–16A). Gene knockout experiments in mice indicate that the T1R2/T1R3 complex mediates the detection of all sweet compounds except for high concentrations of sugars, which may also be detected by T1R3 alone.

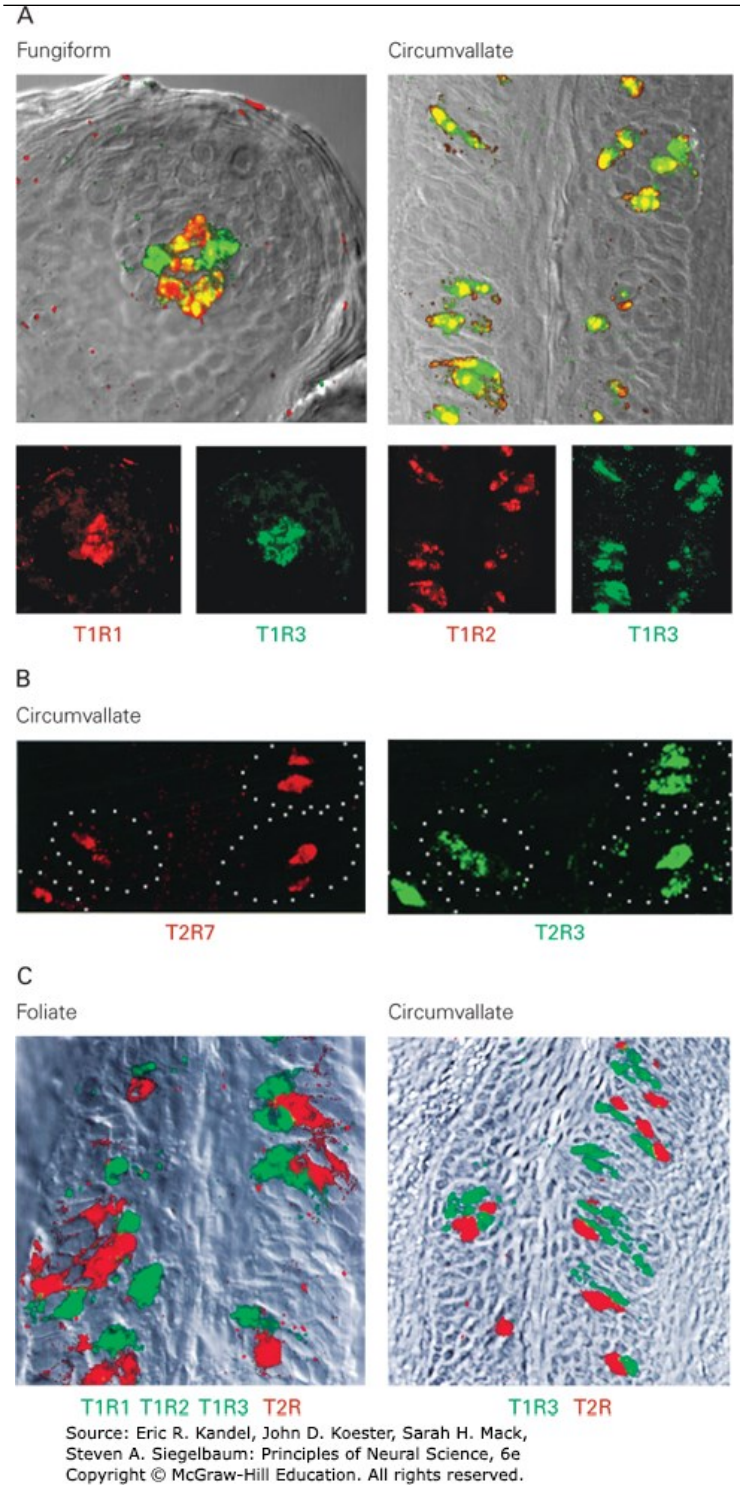
Figure 29–16

(Right) **Expression of T1R and T2R receptors on the tongue.** Sections of mouse or rat tongue were hybridized to probes that label T1R or T2R mRNAs to detect their sites of expression in taste cells.

A. The T1R3 receptor is expressed in taste cells of all three types of papillae. However, T1R1 is found mostly in fungiform papillae, whereas T1R2 is located predominantly in circumvallate (and foliate) papillae. Overlap between sites of expression appears as yellow cells in the micrographs at the top. The T1R1-T1R3 umami receptor is more frequently found in fungiform papillae, whereas the T1R2-T1R3 sweet receptor is more frequently found in circumvallate and foliate papillae. (Reproduced, with permission, from Nelson et al. 2001.)

B. A taste cell that detects bitter tastants can express several variants of T2R receptors. Here, probes for T2R3 and T2R7 labeled the same taste cells in circumvallate papillae. (Reproduced, with permission, from Adler et al. 2000.)

C. The T1R and T2R receptors are expressed in different taste cells. Taste cells labeled by a T1R3 probe or mixed T1R probes (**green**) did not overlap with cells labeled by a mixture of T2R probes (**red**). (Reproduced, with permission, from Nelson et al. 2001.)



Source: Eric R. Kandel, John D. Koester, Sarah H. Mack, Steven A. Siegelbaum: Principles of Neural Science, 6e

Umami Taste Receptor

Umami is the name given to the savory taste of monosodium glutamate, an amino acid widely used as a flavor enhancer. It is believed that the pleasurable sensation associated with umami taste encourages the ingestion of proteins and is thus evolutionarily important for nutrition.

The receptor for umami taste is a complex of two T1R receptor subunits: T1R1, specific to the umami receptor, and T1R3, present in both sugar and umami receptors (Figure 29–14). In mice, the T1R1/T1R3 complex can interact with all L-amino acids (Figure 29–15B), but in humans it is preferentially

activated by glutamate. Purine nucleotides, such as inosine 5′-monophosphate (IMP), are often added to monosodium glutamate to enhance its pleasurable umami taste. Interestingly, in vitro studies demonstrated that IMP potentiates the responsiveness of T1R1/T1R3 to L-amino acids, acting as a strong positive allosteric modulator of the receptor (Figure 29–15B).

Taste cells with both T1R1 and T1R3 are concentrated in fungiform papillae (Figure 29–16A). Studies in genetically engineered mice in which individual T1R genes have been deleted indicate that the T1R1/T1R3 complex is solely responsible for umami taste, whereas T1R2/T1R3 is solely responsible for sweet taste. As expected, a genetic knockout of T1R1 selectively abolishes umami taste, a knockout of T1R2 specifically abolishes sweet taste, while a knockout of T1R3 eliminates both sweet and umami taste (exactly as predicted, given that it is a common subunit of both the umami and sweet taste receptors).

Sweet and umami receptors differ significantly among different species. Most interestingly, different T1R subunits have been lost in some species, likely reflecting their evolutionary niche and diet. For example, the giant panda, which feeds almost exclusively on a bamboo diet, lacks a functional umami receptor. On the other hand, domestic cats, tigers, and cheetahs do not have a functional sweet receptor, whereas vampire bats that feed on a blood diet have mutations that have eliminated both sweet and umami functional receptors.

Bitter Taste Receptor

Bitter taste is thought to have evolved as an aversive signal of toxic molecules. Bitter taste sensation is elicited by a variety of compounds, including caffeine, nicotine, alkaloids, and denatonium, the most bitter-tasting chemical known (this compound is sometimes added to toxic products that are odorless and tasteless to prevent their ingestion).

Bitter tastants are detected by a family of approximately 30 G protein–coupled receptors called T2Rs (Figure 29–14). However, different animal species contain different numbers of bitter receptors (varying from just a handful in the chicken genome to over 50 in the western clawed frog; humans have 28 T2R genes). These receptors recognize bitter compounds that have diverse chemical structures, with each T2R tuned to detect a small number of bitter compounds (Figure 29–15C). The T2R receptors recognize chemicals with high-affinity binding in the micromolar range, allowing detection of minute quantities of harmful compounds. A single taste cell expresses many, probably most, types of T2R receptors (Figure 29–16B). This arrangement implies that information about different bitter tastants is integrated in individual taste cells. Because different bitter compounds are detected by the same cells, all these compounds elicit the same perceptual bitter taste quality. The degree of bitterness might be caused by a compound's effectiveness in activating bitter taste cells.

Interestingly, genetic differences in the ability to perceive specific bitter compounds have been identified in both humans and mice. For example, humans are either super-tasters, tasters, or taste-blind to the bitter chemical 6-n-propylthiouracil. It was by mapping variation in this trait to specific chromosomal loci, and then by searching for novel G protein–coupled receptor genes within that chromosomal interval, that the T2R receptors were first identified. In the case of 6-n-propylthiouracil detection, the gene responsible for the genetic difference has proven to be a particular T2R gene. Thus, some bitter compounds may be recognized predominantly by only one of the approximately 30 T2R receptor types.

Taste cells expressing T2R receptors are found in both foliate and circumvallate papillae in mice (Figure 29–16C). A given taste cell expresses either T2R or T1R receptors (ie, one taste cell–one receptor class), but a single taste bud can contain taste cells of all types (eg, sweet, umami, bitter). Such mixing of cells accords with the observation that a single taste bud can be activated by more than one class of tastant; for example, sweet as well as bitter.

Salty Taste Receptor

Salt intake is critical to maintaining electrolyte balance. Perhaps because electrolytes must be maintained within a stringent range, the behavioral response to salt is concentration dependent: Low salt concentrations are appetitive, whereas high salt concentrations are aversive. How does the response to salt change based on concentration? It turns out that multiple taste cells detect salt. The essential salt taste receptor cell uses the epithelial sodium channel ENaC (see Figure 29–14). These specialized salt taste receptors are distinct from sweet, bitter, or umami receptors. At much higher salt concentrations, some bitter and sour taste cells also respond to salt, although the molecular details of detection have not been determined. Therefore, appetitive concentrations of salt drive responses via the ENaC salt taste receptor in the salt-sensing cells, whereas high salt concentrations activate the bitter and sour cells and thus trigger behavioral aversion.

Sour Taste Receptor

Sour taste is associated with acidic or fermented foods or drink. As with bitter compounds, animals are innately averse to sour substances, suggesting that the adaptive advantage of sour taste is avoidance of spoiled foods. Sour, like the other 4 taste qualities, is also detected by its own type of taste receptor cells (Figure 29–14). The ion channel Otopetrin-1 (Otop1), a proton-selective channel normally involved in the sensation of gravity in the vestibular system, is the sour-sensing ion channel in the taste system. As expected, a knockout of Otop1 in mice eliminated acid responses from sour taste receptor cells. Furthermore, mice engineered to express Otop1 in sweet taste receptor cells now have sweet cells that also respond to sour stimuli, demonstrating that this channel is sufficient to confer acid sensing.

Molecular-genetic studies have demonstrated that the different taste modalities are detected by distinct subsets of taste cells. As we have seen, a combination of T1R1 and T1R3 is responsible for all umami taste, and a combination of T1R2 and T1R3 is needed for all sweet taste detection except for the detection of high concentrations of sugars, which can be mediated by T1R3 alone. The T1R1 and T1R2 receptors are expressed by separate subsets of taste cells, indicating that the detection of sweet and umami tastants is segregated. Similarly, receptors and molecular markers uniquely define bitter, low salt, and sour taste cells.

A dramatic demonstration that each taste quality is detected by a different category of taste cells comes from studies of mice lacking a specific taste receptor gene or cell type. These studies showed that the loss of one taste modality did not affect the others. For example, mice in which sweet cells have been genetically ablated do not detect sugars but still detect amino acids, bitter compounds, salts, and sour compounds. Similarly, mice engineered to lack specific taste receptors cannot detect the corresponding tastants. For instance, mice lacking selective bitter receptors are not responsive to the corresponding bitter tastants, and mice lacking ENaC cannot detect the taste of salt. These types of studies have shown that different tastes are detected by different receptors expressed in different classes of taste cells that drive specific behaviors.

Studies in mice further indicate that it is the taste cells rather than the receptors that determine the animal's response to a tastant. The human bitter receptor T2R16 recognizes a bitter tastant that mice cannot detect. When this receptor was expressed in mouse taste cells that normally express T2R bitter receptors, the ligand caused strong taste aversion. However, when that receptor was expressed in cells that express the T1R2/T1R3 sweet complex (ie, sweet cells), the bitter ligand elicited strong taste acceptance. These findings showed that innate responses of mice to different tastants (sweet and bitter in this example) operate via labeled lines that link the activation of different subsets of taste cells to different behavioral outcomes.

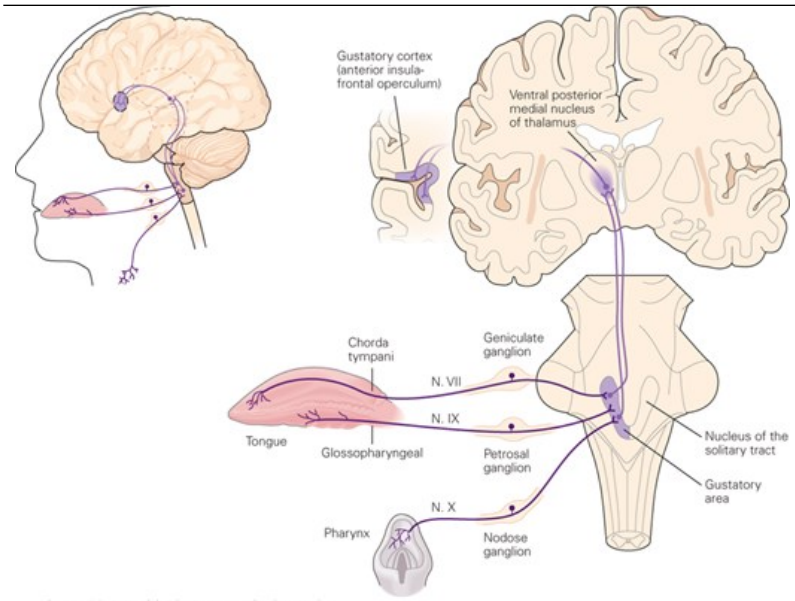
Gustatory Information Is Relayed From the Periphery to the Gustatory Cortex

Each taste cell is innervated at its base by the peripheral branches of the axons of primary sensory neurons (Figure 29–13). Each sensory fiber branches many times, innervating several taste cells within taste buds. The release of neurotransmitter from taste cells onto the sensory fibers induces action potentials in the fibers and the transmission of signals to the sensory cell body.

The cell bodies of gustatory sensory neurons lie in the geniculate, petrosal, and nodose ganglia. The peripheral branches of these neurons travel in cranial nerves VII, IX, and X, while the central branches enter the brain stem, where they terminate on neurons in the gustatory area of the nucleus of the solitary tract (Figure 29–17). In most mammals, neurons in this nucleus transmit signals to the parabrachial nucleus of the pons, which in turn sends gustatory information to the ventroposterior medial nucleus of the thalamus. In primates, however, these neurons transmit gustatory information directly to the taste area of the thalamus.

Figure 29–17

The gustatory system. Tastants are detected in taste buds in the oral cavity. Taste buds on the tongue and pharynx are innervated by the peripheral fibers of gustatory sensory neurons, which travel in the glossopharyngeal, chorda tympani and vagus nerves and terminate in the nucleus of the solitary tract in the brain stem. From there, taste information is relayed through the thalamus to the gustatory cortex as well as to the hypothalamus.



From the thalamus, taste information is transmitted to the gustatory cortex, a region of the cerebral cortex located along the border between the anterior insula and the frontal operculum (Figure 29–17). The gustatory cortex is believed to mediate the conscious perception and discrimination of taste stimuli. The taste areas of the thalamus and cortex also transmit information both directly and indirectly to the hypothalamus, which controls feeding behavior and autonomic responses.

Large-scale calcium imaging revealed that some neurons in the gustatory cortex respond preferentially to one taste modality, such as bitter or sweet. These neurons are localized in segregated cortical fields or hot spots. Interestingly, using a light-activated ion channel to activate neurons in the sweet hot spot elicits innately attractive responses. In contrast, activation of the bitter hot spot evokes suppression of licking and strong aversive orofacial responses, mimicking what is often seen in response to bitter tastants. These experiments showed that direct control of primary taste cortex can evoke specific, reliable, and robust behaviors that mimic responses to natural tastants. They also illustrated that the gustatory pathway can activate innate, immediate responses to sweet and bitter chemicals. To demonstrate that these cortically triggered behaviors are innate (ie, independent of learning or experience), similar stimulation experiments were performed in mutant mice that had never tasted sweet or bitter chemicals (the mutation abolished all sweet and bitter signal transduction). Even in these animals, activation of the corresponding cortical fields triggered the expected behavioral response, thus substantiating the predetermined nature of the sense of taste.

Perception of Flavor Depends on Gustatory, Olfactory, and Somatosensory Inputs

Much of what we think of as the flavor of foods derives from information provided by the integration of the taste and olfactory systems. Volatile molecules released from foods or beverages in the mouth are pumped into the back of the nasal cavity (“retronasal passage”) by the tongue, cheek, and throat movements that accompany chewing and swallowing. Although the olfactory epithelium of the nose clearly makes a major contribution to sensations of flavor, such sensations are localized in the mouth rather than in the nose.

The somatosensory system is also thought to be involved in this localization of flavors. The coincidence between taste, somatosensory stimulation of the tongue, and the retronasal passage of odorants into the nose is assumed to cause odorants to be perceived as flavors in the mouth. Sensations of flavor also frequently have a somatosensory component that includes the texture of food as well as sensations evoked by spicy or minty foods and by carbonation.

Insects Have Modality-Specific Taste Cells That Drive Innate Behaviors

Insects have a specialized gustatory system that evaluates potential nutrients and toxins in food. Taste neurons are found on the proboscis, internal mouthparts, legs, wings, and ovipositor, allowing insects to sample the local chemical environment prior to ingestion. As in mammals, only a few different types of taste cells detect different tastes. In the *Drosophila* fly, the different taste cell classes include those that sense sugars, bitter compounds, water, and pheromones. As in mammals, activation of these different taste cells drives different innate behaviors; for example, activation

of sugar cells drives food acceptance behavior, whereas activation of bitter cells drives food rejection. Thus, the basic organization of taste detection is remarkably similar in insects and mammals, despite divergent evolutionary histories.

The taste receptors in insects are not related to vertebrate receptors. Members of the gustatory receptor (GR) gene family participate in the detection of sugars and bitter compounds. The GRs are membrane-spanning receptors that are distantly related to the odorant receptors of the fly. The fly has approximately 70 GR genes, a surprisingly large number considering it has approximately 60 olfactory receptor genes. Different GRs are found in sugar cells versus bitter cells, with many GRs present in a single neuron. In addition to GRs, other gene families participate in insect taste, including variants of ionotropic glutamate receptors and other ion channel classes. Similar to olfactory detection, the gene families involved in taste recognition differ across phyla, demonstrating that the gene families for chemical recognition have evolved independently.

Highlights

1. Odor detection in the nose is mediated by a large family of odorant receptors that number approximately 350 in humans and 1,000 in mice. These receptors vary in protein sequence, consistent with an ability to detect structurally diverse odorants.
2. Individual odorant receptors can detect multiple odorants, and different odorants activate different combinations of receptors. This combinatorial strategy explains how we can discriminate a multitude of odorants and how nearly identical odorants can have different scents.
3. Each olfactory sensory neuron in the nose expresses a single type of receptor. Thousands of neurons with the same receptor are dispersed in the olfactory epithelium and intermingled with neurons expressing other receptors.
4. In the olfactory bulb, the axons of the sensory neurons expressing the same receptor converge in a few receptor-specific glomeruli, generating a map of odorant receptor inputs that is similar among individuals.
5. The axons of olfactory bulb projection neurons project broadly to multiple areas of the olfactory cortex, generating a highly distributed organization of cortical neurons responsive to individual odorants. The olfactory cortex transmits information to many other brain areas.
6. In mice, pheromones can be detected in the nose or in the vomeronasal organ, a structure absent in humans. Signals from the nose and vomeronasal organ travel through different neural pathways in the brain.
7. The olfactory system of the fruit fly *Drosophila melanogaster* resembles that of mammals in many aspects. It uses a large number of diverse olfactory receptors, with one or a few olfactory receptors expressed by each olfactory sensory neuron. Moreover, neurons with the same receptor synapse in a few specific glomeruli in the antennal lobe of the brain. From there, olfactory signals are transmitted to two major brain areas involved in innate versus learned odor responses. The ease of using genetic approaches in fruit flies has enabled rapid study of mechanisms underlying odor coding and behavior.
8. The gustatory system detects five basic tastes: sweet, sour, bitter, salty, and umami (amino acids). Tastants that activate these taste qualities are detected by taste receptor cells located primarily in taste buds on the tongue and palate epithelium. The detection of the five different taste modalities is mediated by different taste receptor cells, each dedicated to one modality.
9. Sweet tastants are detected by a single type of receptor, which is composed of two subunits, T1R2 and T1R3. Umami receptors are related but comprise a combination of T1R1 and T1R3 subunits.
10. Bitter taste receptors constitute a family of approximately 30 related but diverse receptors that vary in ligand specificity. Individual taste receptor cells express many or all bitter receptors.
11. In contrast to sweet, umami, and bitter receptors, which are all G protein–coupled receptors, salty and sour tastes are detected by ion channels: ENaC for salt taste and Otopetrin-1 for sour taste.
12. Taste signals travel from taste buds through cranial nerves from gustatory sensory neurons in the geniculate, petrosal, and nodose ganglia via labeled lines (sweet taste receptor cells to sweet neurons, bitter taste cells to bitter neurons, etc.). They then travel to the gustatory area of the nucleus of the solitary tract and parabrachial nucleus, and from there to the taste area of the thalamus and then the gustatory cortex. The gustatory cortex, in turn, projects to many brain areas, including those involved in motor control, feeding, hedonic value, learning, and memory.

13. The gustatory cortex contains hot spots for sweet and bitter taste, which, when directly stimulated, can elicit behavioral responses similar to those obtained with tastants applied to the tongue.

14. The fruit fly *Drosophila* also has a specialized gustatory system that evaluates potential nutrients and toxins in food. Different classes of taste cells sense sugars, bitter compounds, pheromones, or water. Activation of these different peripheral sensors drives different innate behaviors, such as food acceptance or rejection.

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