The Chemical Senses 4.6

Learning Objectives

- Indicate the location of the olfactory epithelium
- List four classes of cells in the olfactory epithelium and briefly describe their function
- Describe the mechanism of olfactory sensory transduction (G_s mechanism linked to increased Cl^- conductance)
- Explain how increased Cl^- conductance leads to depolarization in olfactory sensory cells
- Describe the postulated function of the vomeronasal organ
- Explain how some "smells" are actually irritants of the trigeminal nerve
- List three types of papillae on the tongue
- Indicate the parts of the tongue and pharynx innervated by the glossopharyngeal nerve (CN IX), facial nerve (CN VII), and vagus nerve (CN X)
- List the five major taste sensations
- Describe how the "hot" taste of peppers is distinguished from the other taste qualities

THE CHEMICAL SENSES INCLUDE TASTE AND SMELL

The adequate stimuli for the chemical senses are environmental chemicals originating outside the body. The chemical senses include taste and smell. Sensing of these environmental chemicals conveys information vital to the survival of the individual, allowing detection of prey or predators in the case of smell or nourishing or poisonous foods in the case of taste. Smell often carries social and sexual signals as well.

TASTE AND OLFACTORY RECEPTORS TURN OVER REGULARLY

Taste and olfactory receptors line epithelia that are regularly exposed to potentially noxious materials. Because of this exposure, most epithelial cells are regularly sloughed off and replaced with new cells. The same is true for the taste and olfactory receptors. Olfactory receptors turn over every 4–8 weeks. Since the taste receptors are modified epithelial cells, this ability is not surprising. Olfactory cells, on the other hand, are true neurons whose cell bodies are located in the olfactory mucosa and which project axons directly to the olfactory bulb in the brain. Nevertheless, these olfactory neurons are continually replaced throughout life. Basal cells in the olfactory epithelium undergo mitosis to produce new olfactory receptor cells that must grow new axons into the olfactory bulb and make new connections there.

THE OLFACTORY EPITHELIUM RESIDES IN THE ROOF OF THE NASAL CAVITIES

The olfactory epithelium consists of two patches, each with areas of about 5 cm^2, located in the roof of the nasal cavities. The epithelium's surface is defined by a thin perforated bony plate, the cribriform plate, that separates the nasal cavities from the brain. The plate extends horizontally in a plane just below the eyes. A secondary area of olfaction, the vomeronasal organ, lines the turbinates in the nasal cavity. It appears to be sensitive to pheromones and may be involved in sexual function. Figure 4.6.1 shows the location of the olfactory epithelium.

OLFACTORY RECEPTOR CELLS SEND AXONS THROUGH THE CRIBRIFORM PLATE

Figure 4.6.2 illustrates the cells of the olfactory epithelium. They include olfactory receptor cells, supporting cells, basal cells, and secreting cells. The olfactory receptor cells are those that directly respond to odorants, the volatilized chemicals present in the inhaled air that passes by the olfactory epithelium. The molecular shape of the odorants is the adequate stimulus for the modality of olfaction. The olfactory receptor cells are bipolar nerve cells that extend a single dendrite to the surface of the epithelium where it enlarges to form a knob. From this knob, some 5–20 cilia protrude into the layer of mucus that coats the epithelium. The axon extends through the cribriform plate and travels on to make contact with secondary neurons in the main olfactory bulb, which is a specialized region below the frontal lobe, but not part of the cerebral cortex. Thus these olfactory receptor cells are neurons and are called **olfactory sensory neurons** (OSN).

Supporting cells fill in the gaps between the olfactory receptor cells and form a continuous sheet of epithelial cells. They are often called **sustentacular cells**, which literally means "sustaining cells." **Basal cells** are pluripotent stem cells that produce new olfactory receptor

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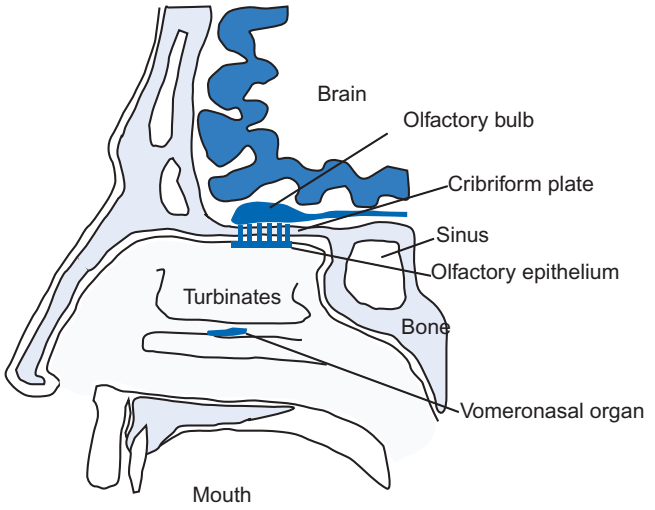

FIGURE 4.6.1 Anatomical location of the olfactory epithelium. The sensors that detect odors lie in the nasal epithelium. They send processes through a perforated bony structure, the cribriform plate, to make connections within the olfactory bulb. The olfactory bulb then sends nerve fibers to the brain for the conscious perception of odors.

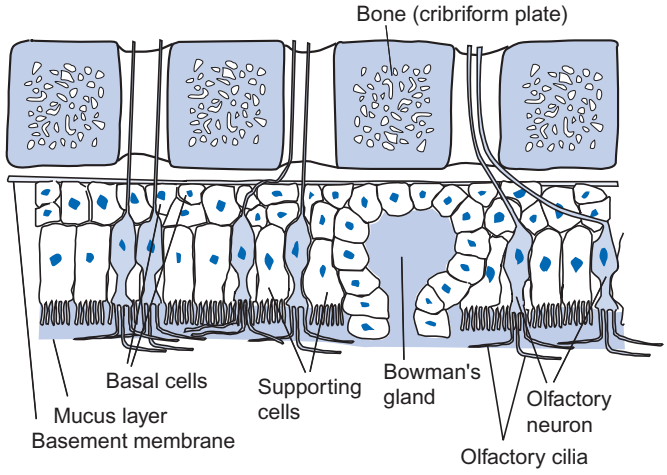

FIGURE 4.6.2 Olfactory epithelial cells. The olfactory epithelium contains olfactory neurons which send an axon through the cribriform plate to make contact with cells in the olfactory bulb. The olfactory neurons are supported by other cells called supporting cells or sustentacular cells. Interspersed among the neurons and supporting cells are secretory glands organized into Bowman's glands that produce a layer of mucus. The olfactory epithelial cells have olfactory cilia that project into the mucus layer. These cilia have the 9 + 2 arrangement of microtubule doublets but they lack the dynein arms, and so they are not motile. Basal cells along the basement membrane are stem cells that differentiate to form new olfactory neurons.

cells, secretory cells, or supporting cells to replace cells that die. Pluripotent cells are already partially differentiated but remain capable of becoming a variety of cell types. Totipotent cells occur early in embryogenesis and are capable of becoming any cell in the body.

A thin layer of mucus covers the entire olfactory epithelium. This material consists of mucopolysaccharides, antibodies, electrolytes, and a variety of soluble **odorant binding proteins**. **Bowman's glands**, consisting of groups of cells interspersed throughout the olfactory epithelium, produce this mucus. The entire mucus content of the olfactory epithelium is replaced about every 10 min. The mucus layer with its associated odorant binding proteins may concentrate odorants and facilitate their interaction with receptors on the olfactory receptor cells, or aid in the disposal of odorants.

HUMANS RECOGNIZE A WIDE VARIETY OF ODORS BUT ARE OFTEN UNTRAINED IN THEIR IDENTIFICATION

Humans readily recognize a variety of images and assign to them their proper names. Many of us can identify and distinguish among a host of sounds: an oboe is easily distinguished from a clarinet or a violin. We easily recognize voices. However, we often have difficulty identifying an odor even though we know we can smell it and we know that there is something vaguely familiar about it. Dogs, on the other hand, recognize the odors of particular people much like we recognize voices. Our inability to identify odors is probably partly due to a lack of training. When presented with a variety of odorants, people often cannot identify them unless provided with a list of descriptors for those odors. The list prompts correct identifications, suggesting that we are untrained in the association of the odors with their descriptors. Typically humans can recognize 10,000 distinct odors, most being disagreeable.

THE RESPONSE TO SPECIFIC ODORANTS IS MEDIATED BY SPECIFIC ODORANT BINDING PROTEINS

Odorant molecules comprise a diverse set of chemicals. To recognize them, the olfactory system uses a large family of receptors called odorant binding proteins that are G-protein-coupled receptors, as described below. The odorant binding proteins are synthesized by individual olfactory sensory neurons, the receptor cells, and are expressed on their cilia where they are exposed to the odorants. The mouse genome contains some 1300 different genes that code for odorant binding proteins, but each olfactory sensory neuron expresses only one of them. Humans have about 350 intact genes for these olfactory receptors (ORs). Each of these responds to a limited spatial arrangement on a chemical, called its molecular receptive range. A second class of chemosensory receptors, first reported in 2001, are the **trace amine-associated receptors (TAARs)**, which originally were thought to recognize volatile trace amines such as trimethylamine, present in mouse urine. Humans have six distinct TAARs. These reside in cells that express the same G-protein expressed in OR olfactory sensory neurons, so the mechanism of signal transduction is likely to be the same as for the olfactory receptors.

The binding of odorant proteins to their receptor on the olfactory receptor cell cilia activates a G-protein called **Golf**. The α subunit of G_{olf} stimulates adenylyl cyclase, which forms cAMP from ATP. The cAMP binds directly

to cation-specific channels in the olfactory receptor cell membrane, increasing conductance to Ca^{2+} or Na^{+}. These are called cyclic nucleotide-gated channels or CNC. The resulting Ca^{2+} influx raises the local $[Ca^{2+}]$ which, in turn, leads to activation of Cl^{-} channels, TMEM 16B. In most cells, the activation of a Cl^{-} channel, resulting in an increased Cl^{-} conductance, would lead to a hyperpolarization or to a decreased ability to move away from the Cl^{-} equilibrium potential. However, olfactory neurons have an unusually high $[Cl^{-}]$, so that the activation of Cl^{-} channels results in a Cl^{-} efflux. Thus, the combined effect of cation entry and anion exit is a depolarization of the cell. Figure 4.6.3 illustrates these events.

The olfactory neuron returns to its baseline state first by removal of the odorant, probably aided by rapid replacement of the mucus that lines the olfactory epithelium. Soluble odorant binding proteins in the mucus may aid in this disposal. This stops the stimulation of G_{olf}. The α subunit spontaneously hydrolyzes its bound GTP to GDP and reassociates with the $\beta\gamma$ subunit, deactivating adenylyl cyclase. Cyclic AMP phosphodiesterase converts cAMP to AMP, thereby deactivating the cation ion channel. The increased cytosolic $[Ca^{2+}]$ is removed by transport to the extracellular space or by uptake by the endoplasmic reticulum (ER).

THE OLFACTORY RECEPTOR CELLS SEND AXONS TO SECOND-ORDER NEURONS IN THE OLFACTORY BULB

Axons leaving olfactory receptor cells cross the cribriform plate and make contact with second-order olfactory neurons in the main olfactory bulb, which is a specialized region below the frontal lobe, but not part of the cerebral cortex. The second-order neurons are mitral cells and tufted cells. The contacts of the second-order neurons and the primary olfactory receptors form glomeruli, which consist of the grouped axonal processes of a large number of olfactory receptors (some 25,000 per glomerulus) and the apical dendrites of some 100 or so second-order neurons; about one-third of these are mitral cells and two-thirds are tufted cells. Each olfactory receptor contacts several second-order neurons, and each second-order neuron receives several thousand inputs from olfactory receptors. The olfactory bulb includes periglomerular cells and granule cells. Information in the form of nerve impulses travels from the olfactory bulb to the brain and back from the brain. A simplified schematic diagram of these connections is shown in Figure 4.6.4.

EACH GLOMERULUS CORRESPONDS TO ONE RECEPTOR THAT RESPONDS TO ITS MOLECULAR RECEPTIVE RANGE

The olfactory neurons expressing a single odorant binding protein send axons through the cribriform plate to the olfactory bulb where they converge on one or at most a few glomeruli. In at least some cases, the synapses in a single glomerulus contain only processes from a single type of olfactory receptor cell. Because mitral cells and tufted cells have a single primary dendrite that projects to a single glomerulus, the response of the mitral cells reflects the response of the glomerulus they innervate. Figure 4.6.5 shows the response of two mitral cells when the olfactory epithelium was exposed to a variety of disubstituted benzene odorants. Mitral cell A is tuned selectively to benzenes substituted in the para position, whereas mitral cell B responds to disubstituted benzenes with short side chains. Note that both mitral cells respond to para xylene. The molecular receptive range of individual mitral cells corresponds to a set of characteristic structural features that may be shared by a range of odorants.

OLFACTION REQUIRES PATTERN RECOGNITION OVER ABOUT 350 INPUT CHANNELS

As described above, each OSN expresses only one type of OR and the axons of those OSN that express the same ORs converge typically on one or two glomeruli located in the olfactory bulb. Each odorant excites a set of OR that depends on the interaction between the OR and the odorant. Thus each odorant activates an odorant-specific pattern of glomeruli. Identification of an odor becomes the problem of recognizing the pattern of activation of the two-dimensional sheet of glomeruli. This recognition occurs in higher centers.

OLFACTORY OUTPUT CONNECTS DIRECTLY TO THE CORTEX IN THE TEMPORAL LOBE

Mitral cells and tufted cells send their processes to several areas including the anterior olfactory nucleus (AON), the piriform cortex (PC), the cortical amygdala, and the entorhinal complex. These areas traditionally constitute the primary olfactory cortex. However, some of these areas do not contain pyramidal neurons that form distinct layers, and so they are not cerebral cortex. These connections are unique in that they are the only sensory connections that do not travel through the thalamus before making connections in the cortex. These connections in the temporal lobe overlay those of the hippocampus and the amygdala, components of the limbic system, which is important in setting mood and emotional behavior. These are the areas that are responsible for associating emotional response with odors. Presumably these areas are also responsible for the highly evocative experience of memory upon odor sensation. These are the basis of the "involuntary memories" as described by Marcel Proust in "A la Recherce du Temps Perdu" (traditionally translated as "Remembrances of Things Past," but more recently translated as "In Search of Lost Time"). Proust describes eating madeleine cakes dipped in tea and the odors and taste evoke childhood memories of eating such cakes with his aunt, and these involuntary evoked memories

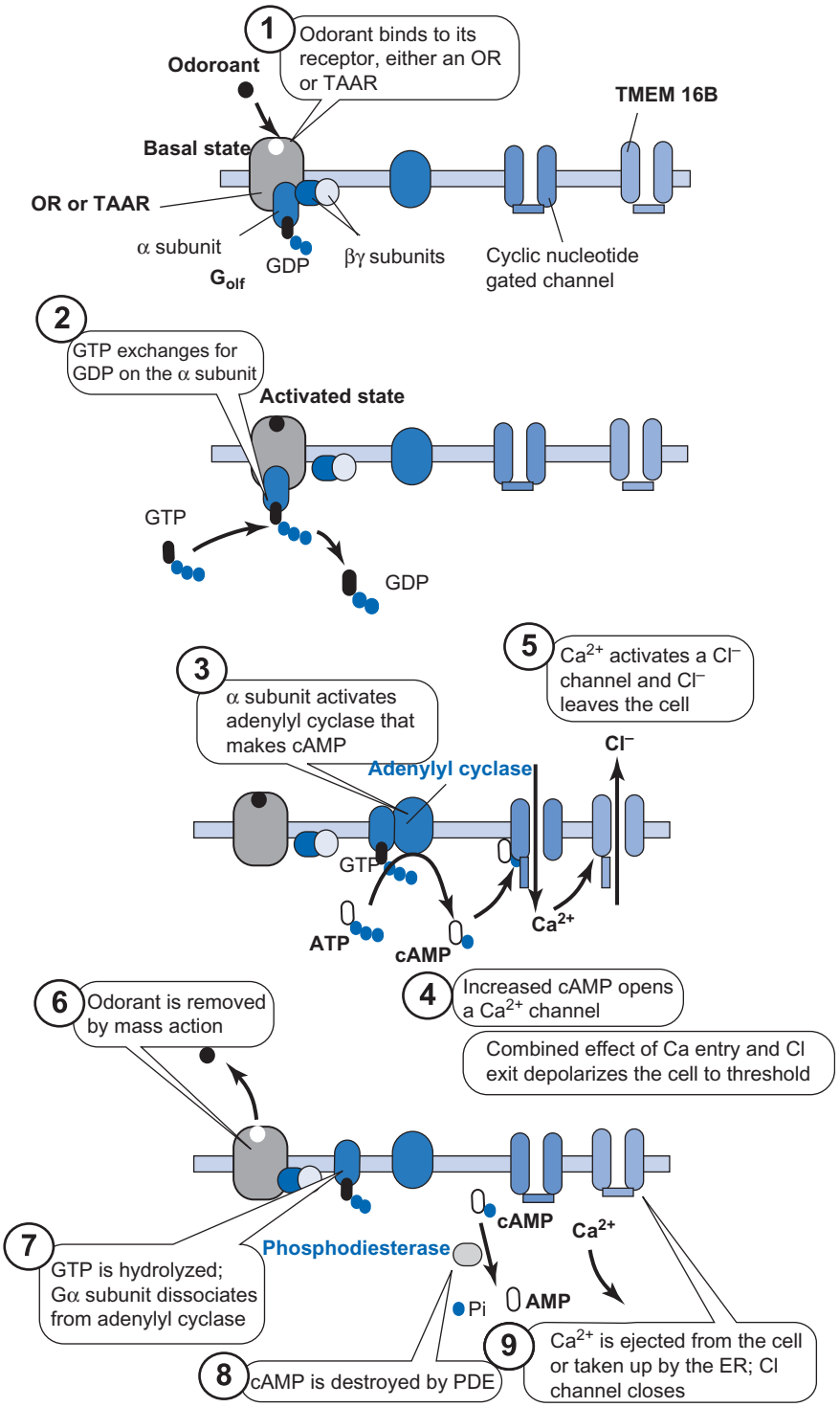

FIGURE 4.6.3 Mechanism of olfactory transduction. Odorants bind to receptor proteins located on the olfactory cilia. These receptor proteins are either an olfactory receptor of a trace amine-associated receptor. The human genome encodes about 350 ORs and only 6 TAARs. Each OSN (olfactory sensory neuron) expresses only one kind of receptor (1). Reception triggers an exchange of GTP for GDP on G_{olf}, a G-protein located in these cells (2). GTP–GDP exchange results in the dissociation of the G_{olf}-α subunit from the βγ subunit. The G_{olf}-α subunit activates adenylyl cyclase to produce cAMP from ATP (3). The cAMP directly activates a cation channel that admits Ca^{2+} into the cell (4). The Ca^{2+} activates a Cl^- conductance pathway which, because of the high $[Cl^-]$ in these cells, produces a Cl^- efflux (5). The cation entry and anion exit produce a depolarization to threshold and the initiation of an action potential on the basal side of the cell toward the cribriform plate. The system is reset by removal of the odorant (by washout and diffusion) (6), inactivation of the Gα subunit by GTP hydrolysis (7), removal of cAMP (by phosphodiesterase) (8), and removal of Ca^{2+} by surface membrane active transport and ER uptake (9).

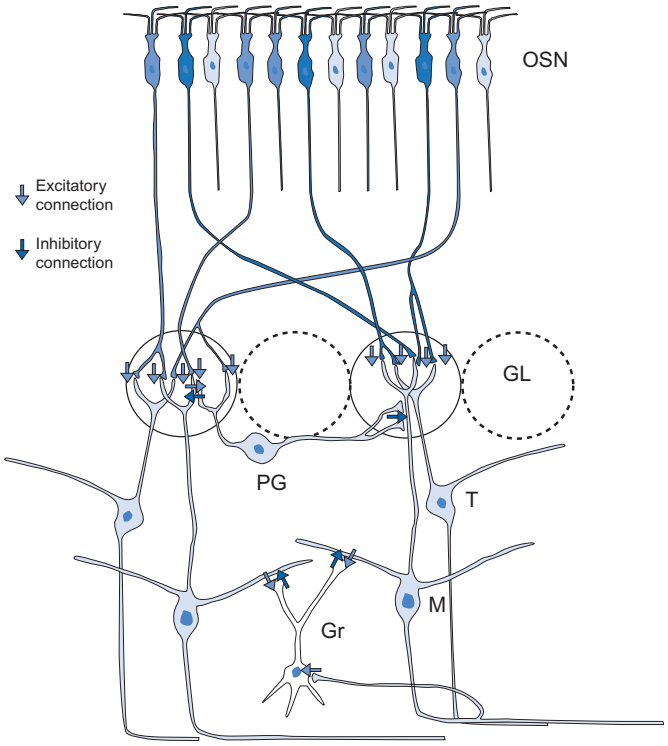

FIGURE 4.6.4 Connections between the olfactory epithelium and the olfactory bulb. Olfactory sensory neurons (OSN) make contact with the dendritic trees of tufted cells (T) and mitral cells (M) in a concentrated area of nerve process called a glomerulus (GL). The individual OSNs each make a single odorant binding protein, and the OSNs making these are randomly distributed within zones of the olfactory epithelium. OSNs making the same kind of odorant binding protein are shown here by the same color. Their processes converge on at most a few glomeruli. Therefore, the response of the mitral cells is tuned to specific odorants. Other cells, such as the periglomerular cells (PG), engage in a kind of lateral inhibition to sharpen the response of the mitral cells. The granule cells (Gr) produce a negative feedback that limits the response of the mitral cells, which form the major output of the olfactory bulb to the olfactory cortex. Light arrows signify excitation; dark arrows signify inhibition. *From K. Mori, H. Nagao, and Y. Yoshihara, The Olfactory bulb: coding and processing of odor molecule information.* Science ***286***: *711—715, 1999.*

bring back additional memories of the town during his forgotten childhood years.

A SECOND OLFACTORY OUTPUT IS THROUGH THE THALAMUS TO THE ORBITOFRONTAL CORTEX

Olfactory output is also funneled through the thalamus to the orbitofrontal cortex. These connections are shown schematically in Figure 4.6.6. Lesions of this area prevent the conscious perception of odors, so this area may be more important than the primary olfactory cortex for this purpose. The primary olfactory cortex may be more important in odor-related memories and emotional responses. The orbitofrontal cortex is adjacent to the primary taste cortex, so that the overall perception of flavor in a food may be produced by overlapping inputs from these two regions. This is in accord with the subjective experience of the tastelessness of food when you have a cold and cannot smell.

THE DETECTION LIMITS FOR ODORS CAN BE LOW

Only volatile chemicals can be smelled because only volatile materials can enter the nostrils along with the inhaled air. In addition, we can smell only those chemicals that are reasonably water soluble because they must penetrate the mucus layer that covers the olfactory receptor cells. These requirements can be overwhelmed by mass action. The volatility of a chemical describes the relationship between the concentration of chemical in the gas phase in equilibrium with the liquid phase. The higher the concentration of chemical in the liquid phase, the higher its concentration in the gas phase. Similarly, water solubility of a volatile material describes the concentration in the water phase in relation to the concentration in the gaseous phase. Thus increasing the concentration in the gas phase would increase the concentration in the water phase. These physical requirements for odorants explain in part their different thresholds for smell.

Methyl mercaptan, $\mathbf{CH_3SH}$, can be detected in inhaled air at concentrations of 10^{-12} M. Because of its low threshold, methyl mercaptan is added to natural gas, which has no natural odor, so that people can smell it to detect gas leaks.

ADAPTATION TO ODORS INVOLVES THE CENTRAL NERVOUS SYSTEM

Subjective experience tells us that sensations of smell nearly disappear upon continued exposure to odorants. Part of this adaptation occurs at the level of the olfactory receptor cells, whose firing rates decrease 50% after the first few seconds of stimulation. This is partly explained by depolarization block—cells that do not repolarize cannot reset their Na^+ channels from the inactivatable state in order to initiate action potentials. However, the subjective experience is greater than this, implying that at least some of the adaptation is due to central nervous system (CNS) processing. The mechanism for this is postulated to occur through granule cells, another nerve cell type within the olfactory bulb (see Figure 4.6.4). These cells receive input from efferent fibers coming back from the brain in the olfactory nerve. These cells release gamma-amino butyric acid on synapses with tufted cells and mitral cells, inhibiting the output of the these latter two cell types.

SOME "SMELLS" STIMULATE THE TRIGEMINAL NERVE AND NOT THE OLFACTORY NERVE

Some irritants produce a strong sensation that is subjectively akin to smell but operates over separate nerve paths. Ammonia, for example, elicits a strong reaction that is carried by the trigeminal nerve, cranial nerve V. The olfactory nerve is cranial nerve I. The trigeminal nerve also carries motor control for mastication and

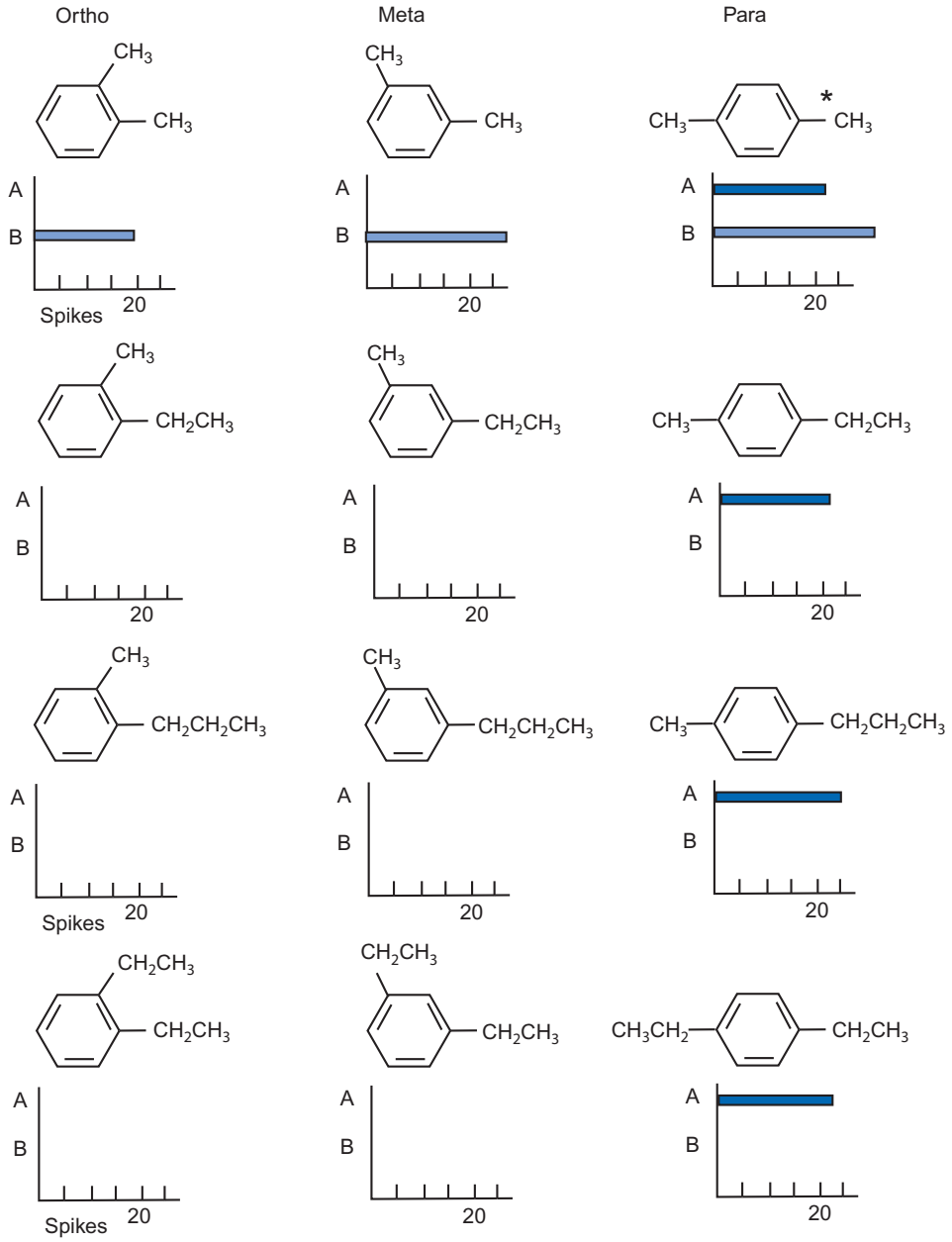

FIGURE 4.6.5 Different mitral cells respond to different molecular features. Responses of mitral cells in the rabbit main olfactory bulb were recorded as the average number of spikes per inhalation cycle for each of the indicated odorants. Two mitral cells were recorded, indicative of the response of two glomerular modules. The molecular structure of the odorants is shown above each graph. Mitral cell A responds to para isomers of disubstituted benzenes (dark bars), whereas mitral cell B responds to disubstituted benzenes with short side chains (light bars). Both cell types respond to para xylene, indicated by the asterisk. Thus mitral cells respond to a range of molecules that incorporate specific structural features. *Modified from K. Mori, H. Nagao, and Y. Yoshihara, The olfactory bulb: coding and processing of odor molecule information.* Science ***286****: 711—715, 1999.*

facial sensory input. Other sensations carried over the trigeminal nerve include those elicited by chlorine, peppermint, and menthol.

HUMANS DISTINGUISH AMONG FIVE PRIMARY TYPES OF TASTE SENSATIONS

Taste performs an essential role in physiology by ensuring the consumption of nourishing foods and the aversion of potentially harmful or noxious foods. Humans discriminate among five primary stimuli: sweet, bitter, sour, salty, and umami. This last is translated as "meaty" or "savory" and is the taste associated with monosodium glutamate (MSG). The entire hedonistic experience of food incorporates additional senses to these five primary modalities, including the hot taste of peppers, coolness of peppermint, texture, weight, and temperature. These additional features are sensed and transmitted separately from the classical sense of taste but become integrated with taste in the hedonistic appreciation of food.

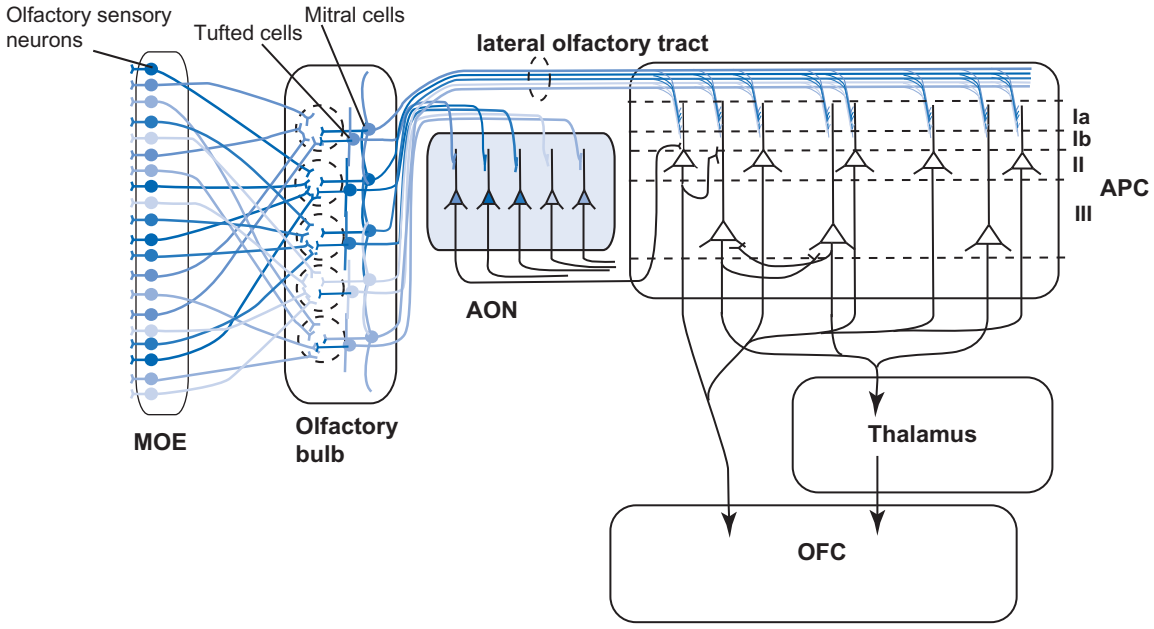

FIGURE 4.6.6 Part of the central connections of the olfactory system. Olfactory sensory neurons (OSN) in the main olfactory epithelium (MOE) make connections in the olfactory bulb in which like OSN converge on one or two glomeruli. These excite tufted cells and mitral cells according to the sensitivity of the OSNs. Mitral and tufted cells send axons to the anterior olfactory nucleus (AON) and to the anterior pyriform cortex (APC) where sensory information is processed further. The APC is cortical, consisting of pyramidal neurons in layers. Pyramidal cells in layer II send axons directly to the orbital frontal cortex (OFC) whereas those in layer III send axons first to the thalamus (submedius nucleus and mediodorsal nucleus, not shown). Cells in the thalamus then send axons to areas of the orbitofrontal cortex.

THE TASTE BUDS ARE GROUPS OF TASTE RECEPTORS ARRANGED ON TASTE PAPILLAE

Taste receptors are modified epithelial cells that are concentrated in specialized structures called taste buds (see Figure 4.6.7). Taste buds are found on the tongue and also distributed throughout the rest of the oral cavity, epiglottis, and esophagus. The taste buds also contain sustentacular or supporting cells and basal cells that divide and differentiate into new taste receptors. Taste receptors die and are replaced after a life span of about 2 weeks. Each taste bud consists of a group of some 50–100 taste receptor cells (TRCs) together with their supporting and basal cells. The cells are arranged like the slices of an orange with a central pore that opens onto the surface of the tongue. Microvilli from the TRCs protrude into the central pore where they sense dissolved chemicals. The taste buds reside on taste papillae. These are larger structures with three distinct varieties that differ with respect to their structure and their location on the tongue (see Figures 4.6.8 and 4.6.9).

Circumvallate papillae are located in the posterior of the tongue and respond to bitter substances such as plant alkaloids, which are often poisonous. As their name implies, these are large, round structures surrounded by a depression or valley. They are innervated by the **glossopharyngeal nerve** or **cranial nerve IX**. There are typically only 10–12 of these in the tongue.

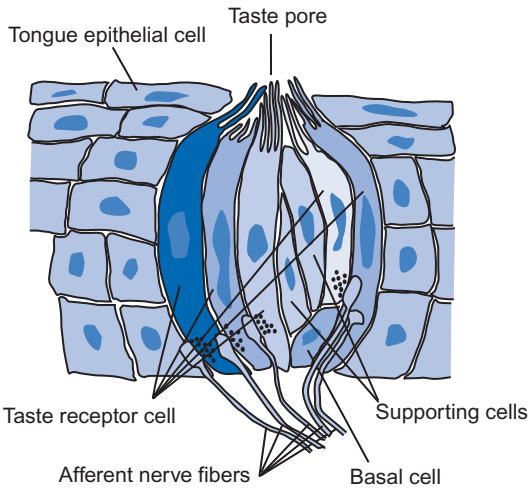

FIGURE 4.6.7 Histology of a taste bud. Taste buds are collections of 50–100 TRCs, basal or stem cells, and supporting cells, arranged something like the slices in an orange. The receptor cells contain synaptic vesicles on their basal sides where the terminus of an afferent sensory neuron makes a synapse. The receptor cells depolarize in response to a tastant, resulting in a cascade of events that eventually cause an action potential in the afferent nerve fiber. Each TRC makes receptors for a single class of tastants, so individual TRCs are tuned to one of each of the primary taste modalities. These are signified by the different colors of each TRC.

The taste buds are located on the sides of the papillae, as many as 250 per papilla.

Several hundred **fungiform papillae** are located in the anterior two-thirds of the tongue and respond best

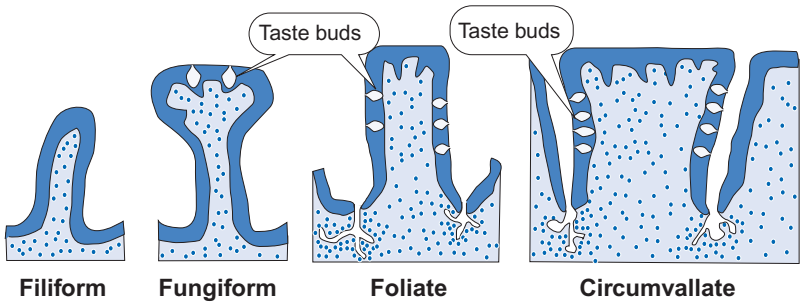

FIGURE 4.6.8 Types of papilla. The filiform papillae are found all over the tongue and contain no taste buds. The fungiform papillae are located anteriorly, have one to five taste buds and are innervated by the facial nerve. The foliate papillae are lateral and posterior, and are innervated by the glossopharyngeal nerve. The few circumvallate papillae are located at the base of the tongue.

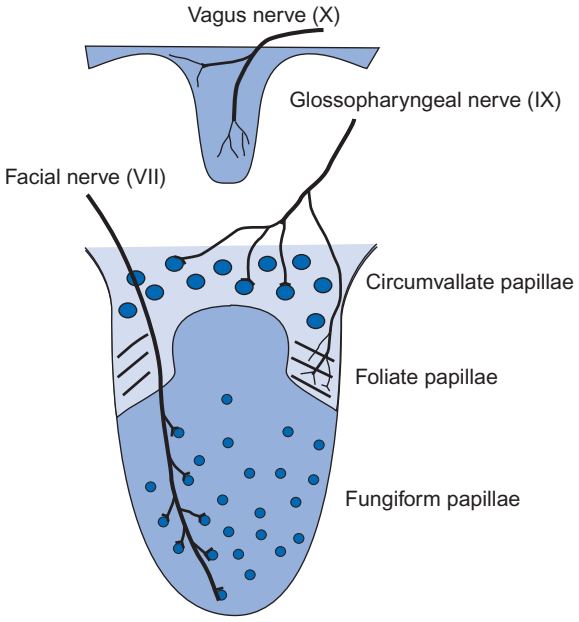

FIGURE 4.6.9 Innervation of the tongue and pharynx. The posterior part of the tongue, near the base, contains 10–12 circumvallate papillae and is innervated by the glossopharyngeal nerve, cranial nerve IX. The foliate papillae are located laterally and posteriorly, and are also innervated by the glossopharyngeal nerve. The anterior two-thirds of the tongue contain mainly fungiform papillae that are innervated by the chorda tympani branch of the facial nerve, cranial nerve VII. The pharynx and epiglottis also have scattered taste buds that are innervated by the vagus nerve, cranial nerve X.

to sweet and salty substances, but also respond to sour. As their name implies, fungiform papillae are shaped like mushrooms. Each papilla has 1-5 taste buds. They send sensory information over the **chorda tympani** branch of the **facial nerve** or **cranial nerve VII**.

Foliate papillae are located in the lateral and posterior edges of the tongue and respond best to sour substances. Once it was believed that particular taste modalities were concentrated in particular areas of the tongue. Although it may be true that some parts of the tongue are more sensitive to particular modalities than other parts of the tongue, all parts of the tongue appear to respond to all five classes of tastants. The lateral and posterior edges are innervated by the glossopharyngeal nerve.

A fourth type of papilla, the filiform papilla, about 2–3 mm long, is located all over the surface of the tongue and is the most abundant type of papilla. These have no taste buds.

The **vagus nerve** innervates taste buds in the posterior pharynx and epiglottis.

TRCs RESPOND TO SINGLE MODALITIES

Recent evidence points to a labeled-line model of sensory reception for taste. In this model, individual TRCs are tuned to respond to a single taste modality to the exclusion of the others. They are also innervated by similarly tuned nerve fibers, so that the excitation of a single TRC induces the firing of its nerve fiber that carries the signal of reception of that modality. The activity is labeled by the kind of cell that produces it.

SALTY TASTE HAS TWO MECHANISMS DISTINGUISHED BY THEIR AMILORIDE SENSITIVITY

Some TRCs possess a highly selective Na^+ channel, the epithelial Na^+ channel or ENaC, on their apical membrane, the one facing the oral cavity. This channel is blocked by amiloride. Because this channel is highly selective for Na^+ over K^+, TRCs possessing this mechanism are also Na^+ selective. Entry of Na^+ into the cell depends on the concentration of Na^+ in the mucosal fluid bathing the cells. It makes an inward current that depolarizes the cell. The depolarization is transmitted electrotonically to the base of the cell where voltage-gated Ca^{2+} channels open, causing Ca^{2+} influx from the extracellular fluid that increases cytosolic $[Ca^{2+}]$ near synaptic vesicles. This causes vesicle fusion with the TRC cell plasma membrane, releasing neurotransmitter. The neurotransmitters in turn change the ionic conductance in the sensory afferent neuron, producing an excitatory postsynaptic potential (EPSP). If the

resulting EPSP reaches threshold, the sensory neuron initiates an action potential. Because fibers innervating TRCs with this mechanism fire selectively to an Na^+ stimulus, they are called N fibers.

The second mechanism for salt sensation also involves an inward current carried by a channel that responds to Na^+, K^+, and NH_4^+. This channel is blocked by another inhibitor, **cetylpyridinium chloride** (**CPC**), but is insensitive to amiloride. Together, both channels appear to explain all of the response to NaCl. Humans have mostly amiloride-insensitive salt taste. Because the amiloride-insensitive component does not distinguish highly between Na^+ and K^+, we can use KCl on the table as a substitute for NaCl. Fibers that innervate TRCs with this mechanism are called **H fibers** (see Figure 4.6.10).

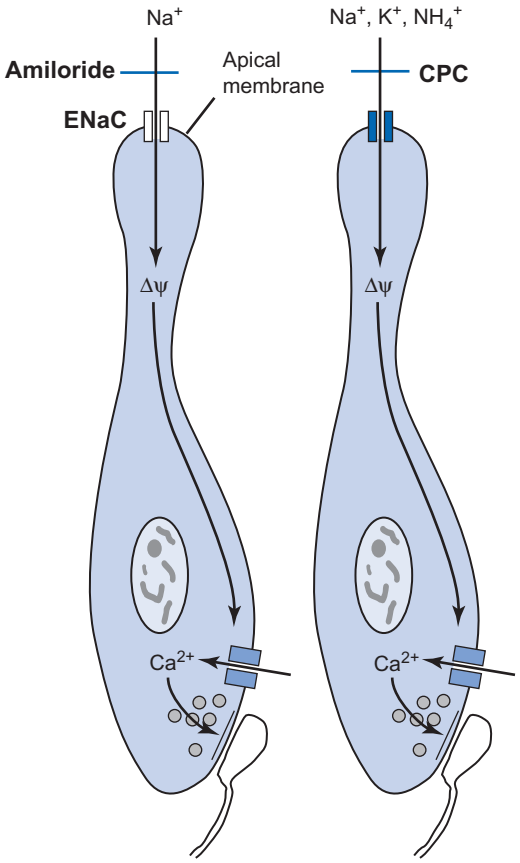

FIGURE 4.6.10 Mechanism of salt taste transduction. In the sodium-selective mechanism, Na^+ enters the cell through an apical Na^+-selective channel, the ENaC. This entry depends directly on the sodium concentration in the fluid bathing the apical surface. This is blocked by amiloride. The resulting depolarization spreads electrotonically to the basal–lateral membrane of the cell where voltage-gated Ca^{2+} channels admit Ca^{2+} depending on the depolarization. The resulting increase in cytosolic $[Ca^{2+}]$ causes fusion of synaptic vesicles with the basal–lateral membrane of the TRC, causing release of neurotransmitter. The neurotransmitter then excites the primary sensory afferent fiber. A second mechanism uses a less selective cation channel which is insensitive to amiloride but is blocked by CPC. The resulting depolarization causes the same events as Na^+ influx through ENaC.

SOUR TASTE DEPENDS ON TRC CYTOSOLIC pH

The apical membrane of sour TRCs has an H^+ channel that allows entry of H^+ ions. This channel is not yet identified. Exposure of these cells to an acid solution causes the cytosolic pH to decrease (because $[H^+]$ increases) and this is presumably coupled to Ca^{2+} entry near the synapse. This Ca^{2+} entry may be linked to depolarization caused by H^+ entry or by its activation of Na^+ channels, or inhibition of K^+ channels. Weak acids cause excitation of sour taste receptors by a different mechanism: they cross the apical membrane in the neutral, nonionized form which then forms H^+ inside the cell. Thus the increased $[H^+]$ itself is the initial signal. The precise cascade of events is not yet clear. These TRCs have a Na^+–H^+ exchanger located on the basolateral surface that is activated by cytosolic Ca^{2+}. This can explain the adaptation to sour substances: acidic solutions presented to the apical membrane increase the cytosolic $[H^+]$ which then increases cytosolic $[Ca^{2+}]$. The increased $[Ca^{2+}]$ increases the rate of H^+ exchange out of the cell, bringing the cytosolic pH back toward normal and reducing the activity of the receptor. Thus the system naturally adapts. Figure 4.6.11 illustrates the sour taste mechanism.

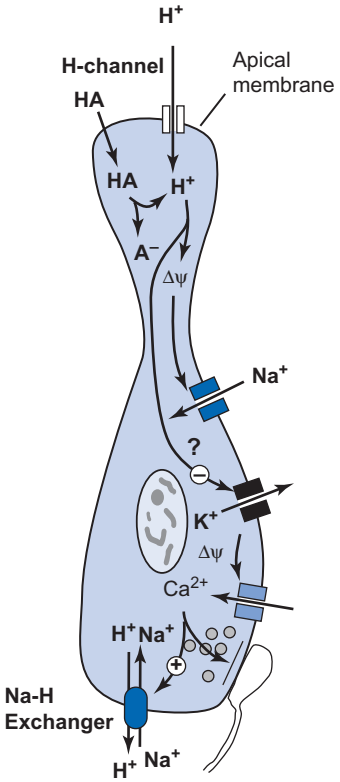

FIGURE 4.6.11 Mechanism of sour taste transduction. TRCs for sour taste respond to the intracellular pH. Decreases in pH result in fusion of vesicles and release of neurotransmitter to the primary sensory afferent neurons. Increasing $[H^+]$ in the apical solution or exposure to high concentrations of weak acid, HA, both lead to an increased cytosolic $[H^+]$, which somehow is linked to Ca^{2+} entry into the cell and fusion of synaptic vesicles with the TRC's plasma membrane. Adaptation to the sour taste occurs by the activation of efflux pathways for H^+. Activation of the Na–H exchange protein is shown.

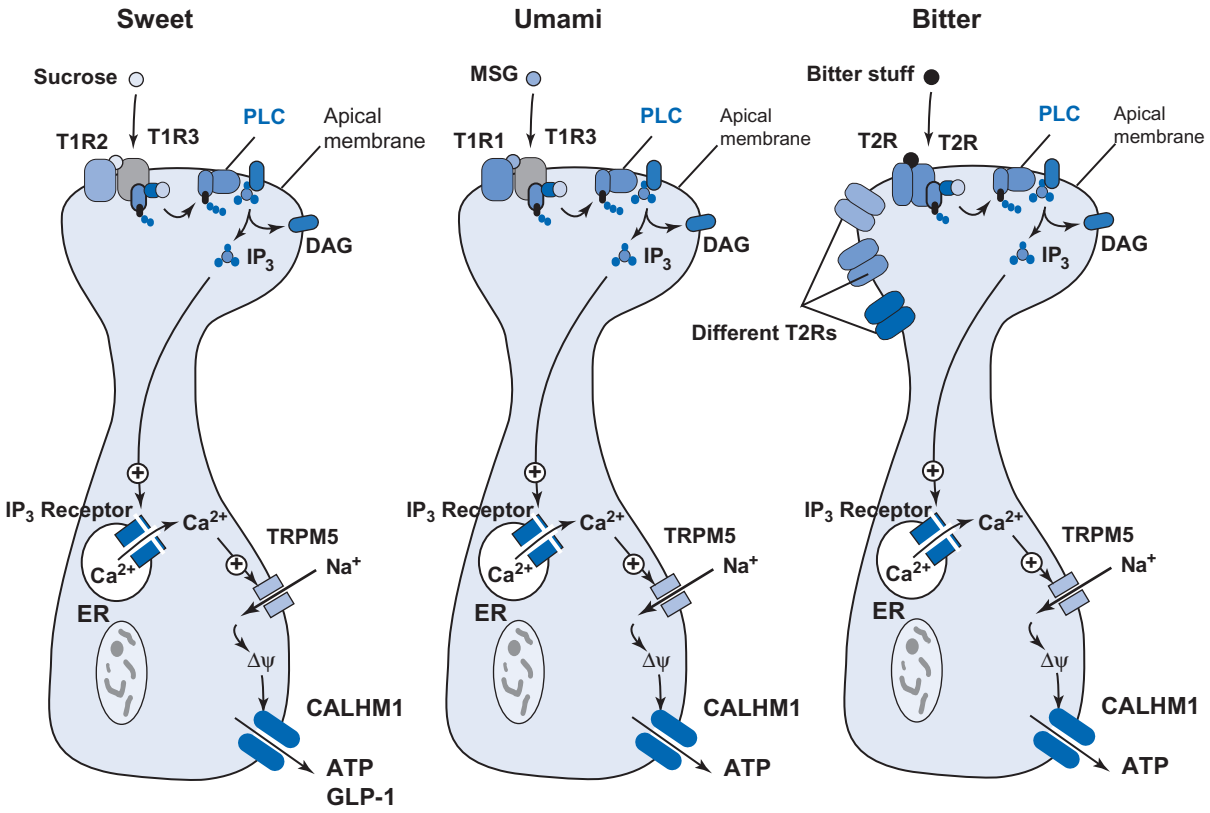

FIGURE 4.6.12 Mechanism of sweet, umami, and bitter tastes. All three of these work through G-protein-coupled receptors. In the case of sweet, a heterodimer composed of T1R2 and T1R3 senses sweet materials in the solution on the surface of the tongue. This is coupled to a G-protein that activates phospholipase C to hydrolyze phosphatidyl inositol 4,5-bisphosphate to DAG and IP3 which binds to an IP3-receptor on the ER, releasing Ca^{2+} ions into the cytoplasm. The increased $[Ca^{2+}]$ activates a TRPM5 which increases conductance for Na^{+}, producing a depolarization. The depolarization results in the release of glucagon-like peptide 1 (GLP-1) and ATP in the case of sweet taste and probably ATP in the case of umami and bitter taste. Release of these neurotransmitters seems to not involve vesicle fusion but may involve a pore provided by CALMH1, for calcium homeostasis modulator. This basic signaling cascade also occurs for umami and bitter tastes, except the surface taste receptors are different. In the case of umami, the receptors on the surface of the cell, on the microvilli at the central pore, are heterodimers of T1R1 and T1R3. In the case of bitter taste, about 25 different T2R genes are expressed, many if not all on a single TRC. All of the T2R receptors eventually produce the same subjective taste of "bitter."

SWEET, BITTER, AND UMAMI TASTE ARE TRANSDUCED BY THREE SETS OF G-PROTEIN-COUPLED RECEPTORS

Sweet, bitter, and umami tastes share the common feature of activating a GPCR that uses a G_q mechanism to activate a channel called TRPM5 for transient receptor potential type M5. This downstream signaling pathway is shared by all three modalities. What distinguishes them is the receptors that initiate the cascade. There are three T1 receptors, T1R1, T1R2, and T1R3, and a family of about 25 T2R receptors. T1R3 forms a heterodimer with T1R2 to form the sweet taste receptor, and with T1R1 to form the umami taste receptor. Mice with knockouts of the T1R3 gene do not respond to either umami or sweet tastants; knockouts of T1R2 alone cannot respond to sweet but do respond to umami tastants; knockouts of T1R1 alone cannot respond to umami but respond to sweet. Bitter taste, on the other hand, is enabled by the expression of a family of about 25 different receptors in the T2R family. These form homodimers that respond to bitter tastants. TRCs typically express many and perhaps all of these different receptors in individual cells. Thus many different tastants of considerably different chemical structure produce the same subjective bitter taste. Figure 4.6.12 shows the mechanisms for sweet, bitter, and umami tastes.

THE "HOT" TASTE OF JALAPENO PEPPERS IS SENSED THROUGH PAIN RECEPTORS

The "hot" taste of jalapeno peppers is due to a chemical, capsaicin, that is present in the chili peppers. This compound activates the vanilloid receptor (VR1), a nonselective cation channel found on small unmyelinated fibers (type C fibers and Aδ fibers). These fibers are also activated by pain and heat. Some of these fibers enter the CNS over the trigeminal nerve. This explains the "hot" sensation of chilis that can border on painful and its subjective pungent quality. Other sensations that are carried over the trigeminal nerve include those elicited by peppermint, chlorine, and menthol.

Clinical Applications: Ageusia

The ability to taste things in food or drinks depends on specific chemicals in the food binding to receptors on the taste cells. Many of these receptors are metabotropic, coupled to G-proteins that are linked to intracellular signaling mechanisms that eventually cause the release of neurotransmitters at the basal pole of the taste cells. These receptors are proteins whose amino acid sequence is directed by DNA. Individuals with mutations in the DNA can produce receptors that have reduced affinity for the tastants or the receptors may be absent altogether. Such persons can experience taste deficits. Ageusia means the inability to taste. Specific ageusia refers to the inability to taste a specific chemical. Hypogeusia means that the person has an elevated threshold for detection of tastants—they are less sensitive than normal.

The ability to taste phenylthiocarbamide, PTC, is genetic, and the human population is heterogeneous with respect to this ability. The PTC receptor is a member of the T2R family of bitter taste receptors. Three single nucleotide polymorphisms have been identified, with three single amino acid substitutions. These polymorphisms are pro/ala at amino acid 49; ala/val at amino acid 262; and val/ile at amino acid 296. The ancestral and normal form of the protein is pro–ala–val, and persons with this receptor can taste PTC. Persons homozygous for the ala–val–ile form of the receptor cannot taste PTC or do so at much reduced sensitivity.

Other specific ageusias exist. In a sample of 109 people, some 83% were classified as "normal" tasters for MSG, whereas the remaining 17% were "hypotasters." Because psychophysical studies are difficult to do, multiple testing regimens are employed and classification as a "taster," "hypotaster," or "nontaster" depends on the regimen. Further testing showed a smaller proportion of people who could be regarded as "nontasters."

Ageusia for PTC and MSG are currently the only known representatives of taste blindness in humans.

Clinical Applications: Foreign Chemicals and Endogenous Ligands

The vanilloid receptors are widespread throughout the animal kingdom, but those of birds differ from those of mammals; the birds' VR1 does not respond to capsaicin. It has been postulated that this is an example of coevolution, where one species hones its chemicals to fit the environment partly provided by other species. Plants need to disperse their seeds, and they engage in a variety of mechanisms for doing so. One mechanism is to attract animals who will eat the plants and disperse the seeds in their feces. The seeds must resist digestion themselves. Experiments have shown that chili seeds will not germinate after ingestion by rodents, but they will germinate after being eaten by birds. The "hot" taste of chilis discourages herbivores from feeding on the plant because it is painful, but it does not deter the birds. It is difficult to say which came first: the chili plant that exploits a difference in the VR1 receptors or birds that exploited a difference in their VR1 receptor to harvest a food source unsavory to the rodents.

This prompts the question: why do we have receptors that are sensitive to capsaicin? This question extends to a host of foreign chemicals that have very specific effects on the body. Why do naturally occurring foreign compounds have such specific effects? The final answer to such a question is elusive, of course, but there are two potential answers: (1) plants evolved the synthetic machinery to make these compounds to target our receptors for some effect—usually bad; (2) the effects are entirely accidental and result from the similarity in the shape of the chemicals to some endogenous ligands that we use as part of our normal signaling pathways.

An outstanding example of this is opium. Opium is an extract of the opium poppy, *Papaver somniferum*. It has been used for thousands of years to produce euphoria, analgesia, and sleep, and for relief of coughs. Friedrich Sertürner synthesized codeine and morphine from the poppy plant in 1805. Morphine is named after Morpheus, the Greek god of dreams, and is a potent analgesic (pain reliever). Heroin is synthesized from morphine. The basis of these effects was first illuminated by Candice Pert and Solomon Snyder when they demonstrated that opiates have specific receptors. This brings us back to the question as to why we would have receptors for poppy plant extracts. John Hughes and Hans Kosterlitz found that these receptors responded to two naturally occurring endogenous peptides, named **endorphins** for *endo*genous *morphine*-like substances. Thus the pharmacological properties of morphine are probably entirely accidental, resulting from its ability to bind to receptors at the same site as our endogenous ligands.

Is there an endogenous ligand for the capsaicin receptor? Recent investigations suggest that a chemical called **anandamide** may be an endogenous ligand for the VR1 receptor. This compound is derived from arachidonic acid. Anandamide was originally proposed to be the endogenous ligand for the cannabinoid receptors, CB_1 and CB_2, that respond to the active chemical from marijuana (*Cannabis sativa*), Δ^9-tetrahydrocannabinol. But anandamide stimulates only the CB_1 receptors and another endogenous compound, 2-arachidonoyl-glycerol, fully excites both CB_1 and CB_2 receptors. Anandamide excites the VR1 receptors and may be its endogenous ligand.

TASTE RECEPTORS PROJECT TO THE CORTEX THROUGH THE SOLITARY NUCLEUS AND THE THALAMUS

The TRCs are not neurons, even though they release neurotransmitters, because they have no dendritic of axonal processes. They make synapses onto dendritic processes of primary afferent sensory neurons whose cell bodies reside in three cranial nerve ganglia. The anterior two-thirds of the tongue and the palate are innervated by the facial nerve or cranial nerve VII. The cell bodies for the taste fibers are in the geniculate ganglia. The posterior third of the tongue is supplied by the glossopharyngeal nerve or cranial nerve IX. The cell bodies for this sensory nerve are located in the inferior glossopharyngeal ganglia. The vagus nerve, cranial nerve X, supplies the scattered taste receptors in the throat regions, including the glottis, epiglottis, and pharynx. The cell bodies of the vagus reside in the inferior vagal ganglia.

Sensory fibers from all three of these cranial nerves enter the lateral medulla and make synapses on cells in the gustatory division of the **solitary nucleus** in the medulla. The second-order neurons in the solitary nucleus send fibers up to the **ventral posterior medial nucleus** of the **thalamus**, where they make synapses on third-order neurons. These thalamic neurons then project to the **primary gustatory cortex** located in the insular and orbitofrontal regions.

FLAVOR IS IN THE BRAIN

The overall sensation of flaxor is a mixture of sensations. Mechanical stimuli ("mouth feel"), odors, taste and temperature all figure into the overall perception of flavors. These diverse nervous signals are first integrated in the anterior insular cortex. This core flavor percept is then conveyed to regions of the amygdala, orbitofrontal cortex, and anterior cingulate cortex to produce the final flavor perception. Exactly how this is accomplished is not yet understood.

SUMMARY

The chemical senses include the sense of taste and smell. Both detect foreign chemicals when they interact with receptors at surfaces of the body. Smell detects volatile chemicals in the inhaled air; taste detects dissolved chemicals in food and drink. Because these receptors are on the surfaces that are exposed to noxious chemicals, both the olfactory and the taste epithelium are replaced regularly. The olfactory cells are true neurons, with an axon exiting the base of the cell, crossing the cribriform plate and making synapses in the olfactory bulb. The taste cells are receptor cells that do not produce action potentials, but instead release neurotransmitter onto a primary afferent sensory cell.

Olfactory receptor cells have long cilia that protrude into a mucus layer that is secreted by Bowman's glands in the olfactory epithelium. Odorant binding proteins on the cilia membrane bind odorants and couple to a G_s protein that stimulates adenylyl cyclase and increases cAMP in the olfactory cells. The cAMP activates protein kinase A that phosphorylates a Ca^{2+} channel, activating it. The increased cytoplasmic $[Ca^{2+}]$ activates a Cl^- channel. Because these cells have higher than normal cytoplasmic $[Cl^-]$, opening the channel causes Cl^- to leave, which makes an inward current that depolarizes the cell. The olfactory cell action potentials are further processed in the olfactory bulb and the signal is relayed to the primary olfactory cortex and the orbitofrontal cortex through the olfactory nerve, cranial nerve I. Some odors are actually irritants whose signals pass to the CNS over the trigeminal nerve, cranial nerve V. Examples include ammonium, chlorine, peppermint, and menthol.

Taste receptors are located in taste buds, conglomerates of about 50–100 cells, on taste papillae on the tongue and elsewhere in the pharynx and palate. The facial nerve (cranial nerve VII) innervates the front of the tongue, the glossopharyngeal (cranial nerve IX) innervates the back of the tongue, and the vagus nerve (cranial nerve X) innervates the palate, pharynx, and epiglottis. There are four types of papilla: circumvallate, fungiform, foliate, and filiform. The filiform papillae have no taste buds. There are five primary taste modalities: salty, sour, sweet, bitter, and umami.

Salty taste has two basic mechanisms: Na^+ entry through the amiloride-sensitive ENaC depolarizes the cell. This is highly selective for Na^+. The second mechanism uses a CPC-sensitive channel that lets in Na^+, K^+, and NH_4^+, which depolarizes the cell. This does not distinguish well between Na^+ and K^+. Humans probably have both mechanisms but do not discriminate well between Na^+ and K^+, so K^+ tastes salty.

Sour taste detects the receptor cell's intracellular $[H^+]$. This is coupled to Ca^{2+} entry that releases neurotransmitter onto the afferent sensory nerve. Increased cytoplasmic $[Ca^{2+}]$ activates H^+ efflux mechanisms, so that the tongue adapts to sour taste.

Sweet, bitter, and umami tastes all use G-protein-coupled receptors. There are three T1 receptors: T1R1, T1R2, and T1R3. These form heterodimers that are responsible for the sweet and umami sensing. TRCs expressing T1R2 and T1R3 on their surface respond to sweet tastants; removal of either protein ablates the ability to taste sweet materials. TRCs expressing T1R1 and T1R3 are responsible for the umami taste. TRCs that sense bitter compounds express several members of the T2R receptor family, all of which subjectively appear to be bitter. Each TRC responds to only one taste modality, and thus the sense of taste is a labeled-line mechanism.

The intracellular signal cascade for sweet, bitter, and umami modalities are similar. Binding of tastant to the receptor dissociates the heterotrimeric G-protein, activating phospholipase C that splits phosphatidyl inositol 4,5-bisphosphate to diacylglycerol (DAG) and inositol trisphosphate (IP3). The released IP3 binds to IP3-receptors on the ER, which then form a Ca^{2+} conducting pathway and release Ca^{2+} that is stored in the ER. The increase in cytosolic $[Ca^{2+}]$ activates a transient receptor protein (TRPM5) which increases Na^+ influx,

thereby depolarizing the TRC. The depolarization releases neurotransmitter at the base of the TRC, activating the primary afferent neuron.

The "hot" taste of chili peppers is due to capsaicin, which stimulates small unmyelinated fibers in the trigeminal nerve. Capsaicin excites the vanilloid receptor, VR1.

REVIEW QUESTIONS

1. Where is the olfactory epithelium? What is the cribriform plate? Describe the shape of the olfactory sensory neuron. What is unique about it?
2. How do olfactory sensory neurons get depolarized when odorants bind to their olfactory cilia? How specific is the response?
3. Where do the axons of the olfactory sensory neurons go? Is there a specific glomerulus at which they form synapses? What cells form the output of the olfactory bulb?
4. How many different odorants can humans detect? How many odorant binding proteins do we make?
5. What are the five taste modalities? Are these sensed in particular areas of the tongue?
6. What is a taste bud? Where are they located?
7. What are the four different types of tongue papillae? Do they all have taste buds?
8. Which part of the tongue is innervated by the facial nerve? Glossopharyngeal nerve? Vagus nerve?
9. How is salty taste transduced? Why do both NaCl and KCl taste salty to humans?
10. How is sour taste transduced? Why does it adapt?
11. What is the general mechanism for sweet, bitter, and umami tastes? Why are there multiple receptors for bitter taste but not sweet taste?