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

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

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

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

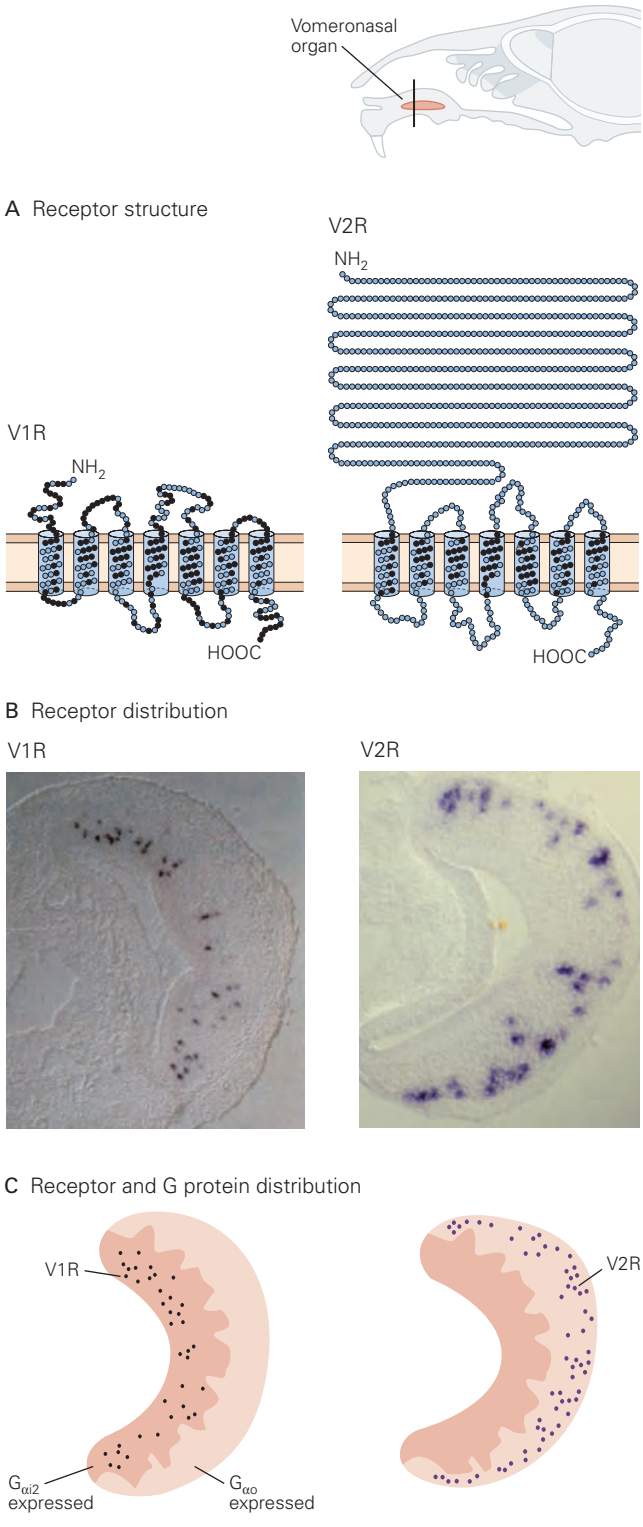

Figure 29–9 (Right) Candidate pheromone receptors in the vomeronasal organ.

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

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

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

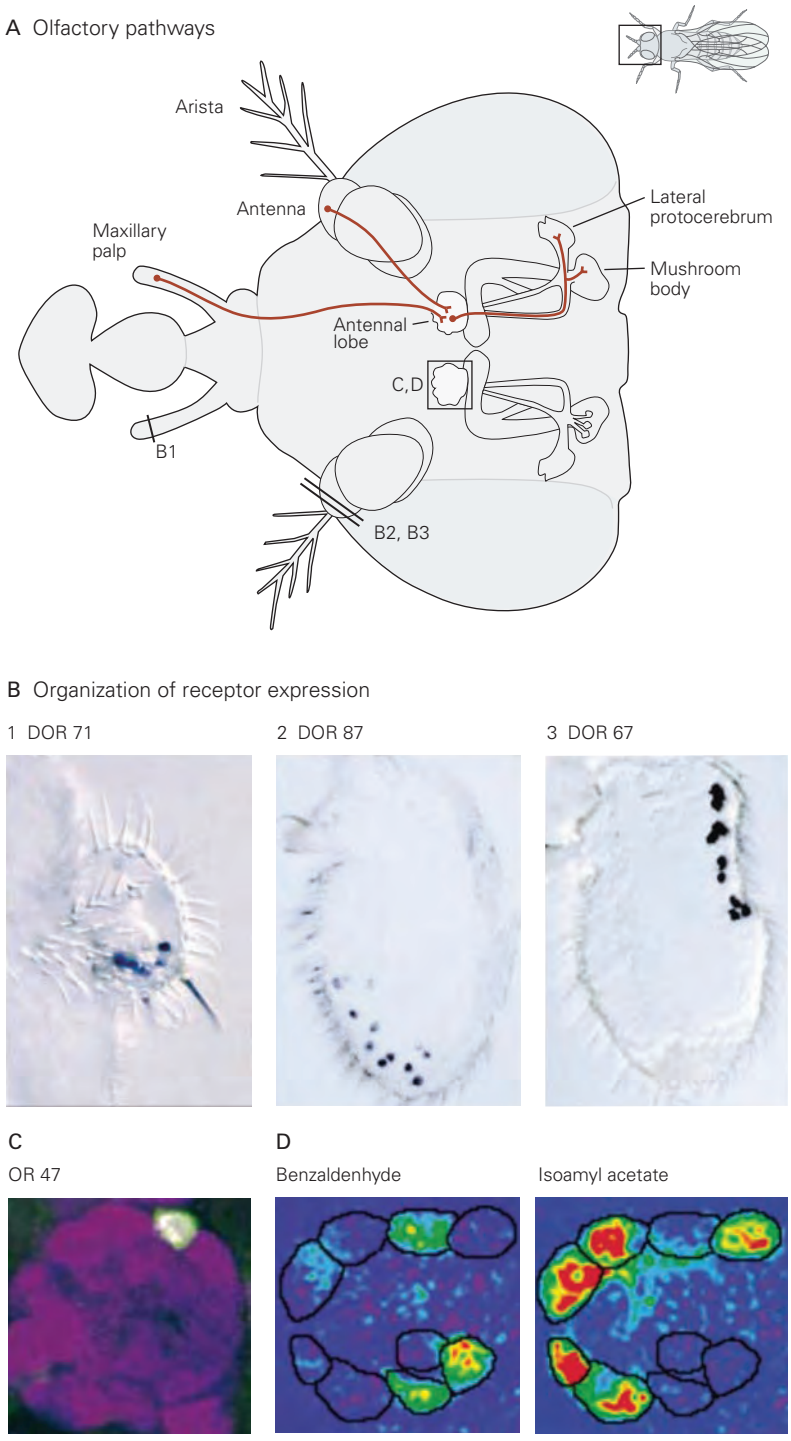

Figure 29–10 Olfactory pathways from the antenna to the brain in *Drosophila*.

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.)

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.

The "one neuron, one receptor" principle observed in vertebrates and insects does not operate in nematodes because the number of neurons is much smaller

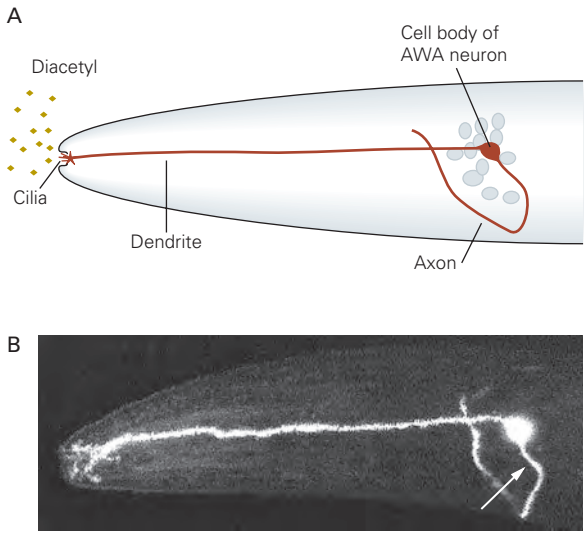

Figure 29–11 The receptor for diacetyl in the *Caenorhabditis elegans* worm.

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.)

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.

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.

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.)

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.

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.

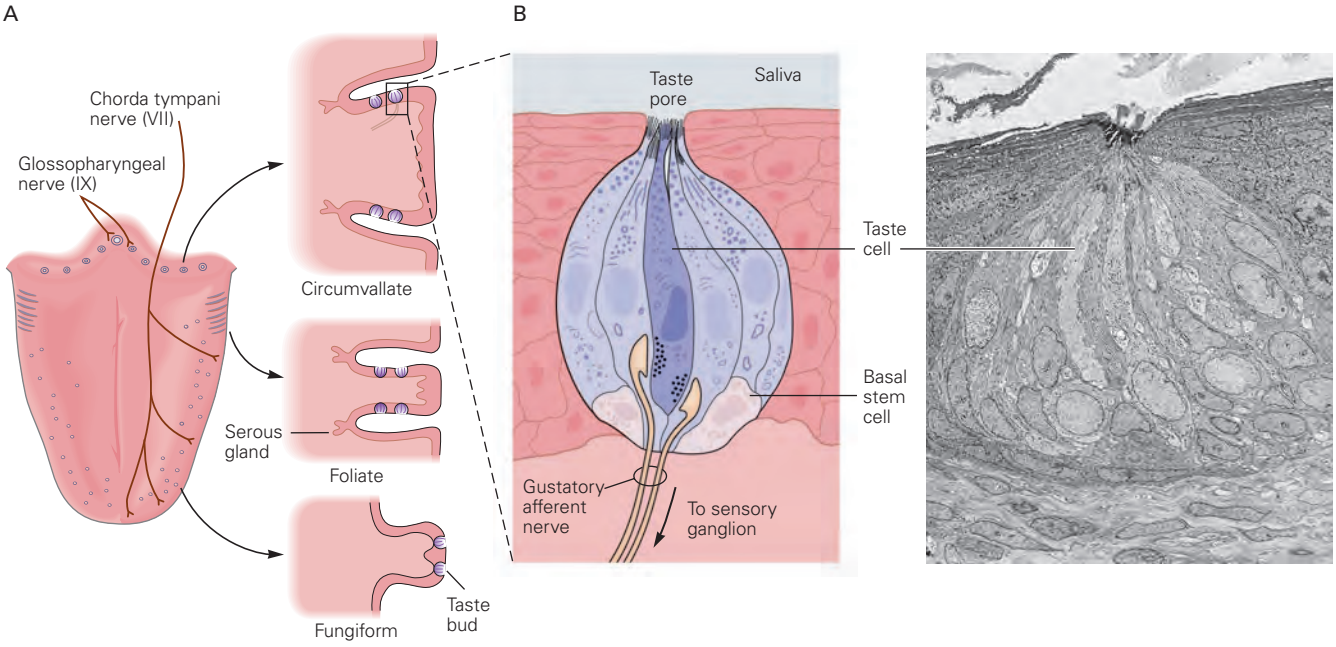

Figure 29–13 Taste buds are clustered in papillae on the tongue.

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.)

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.

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.

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

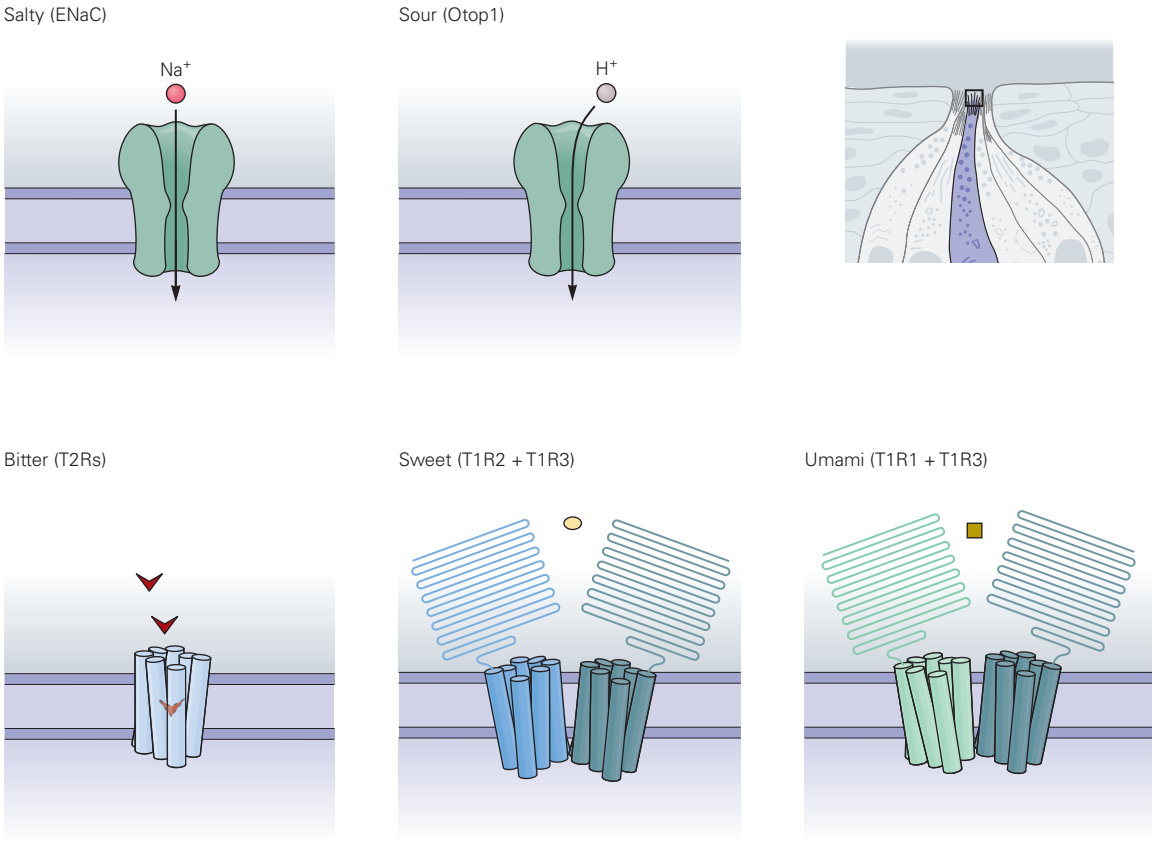

Figure 29–14 Sensory transduction in taste cells. Different taste qualities involve different detection mechanisms in the apical microvilli of taste cells (see Figure 29–13B). Salty and sour tastants directly activate ion channels, whereas tastants perceived as bitter, sweet, or umami activate G protein–coupled 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.

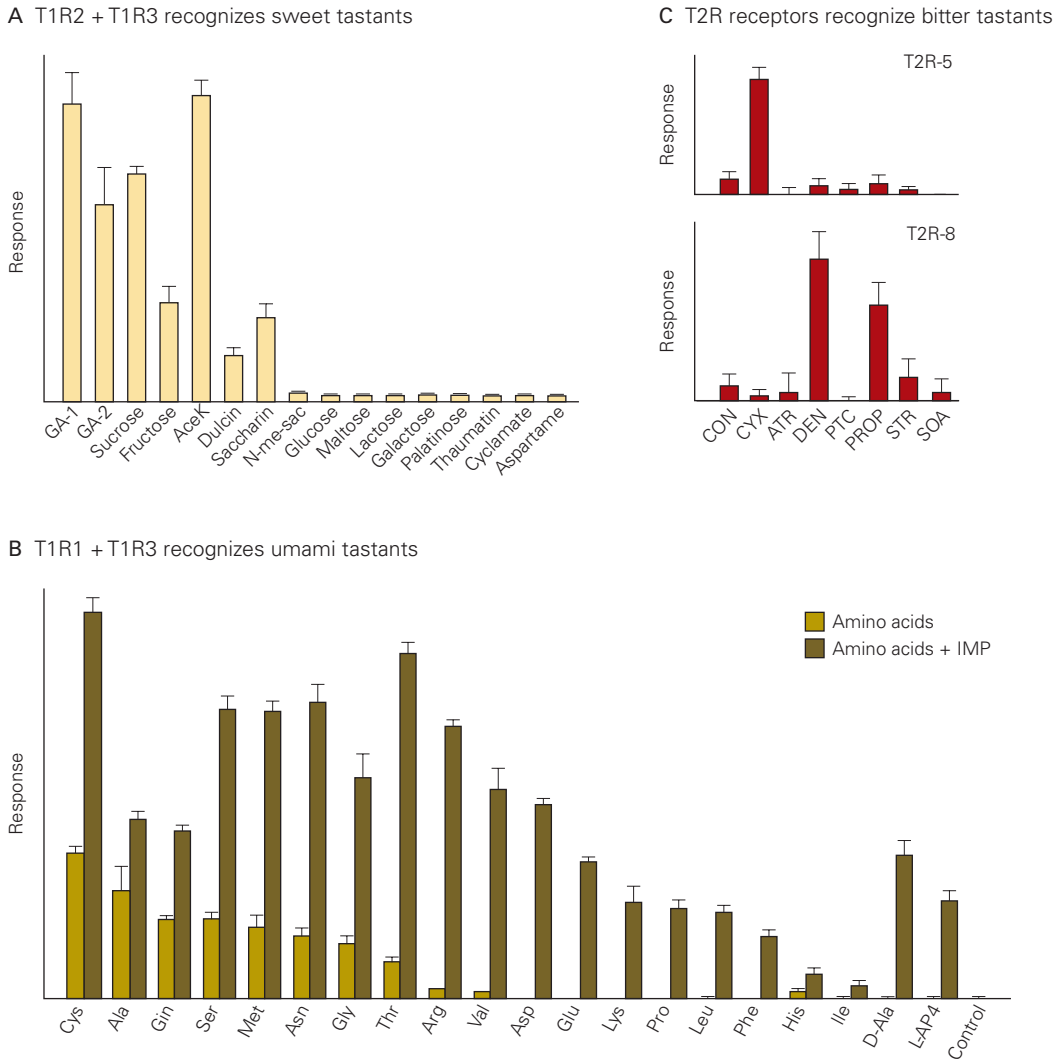

Figure 29–15 Tastants recognized by T1R and T2R receptors. A calcium-sensitive dye was used to test whether T1R and T2R receptors expressed in a tissue culture cell line could detect tastants.

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.)

the detection of all sweet compounds except for high concentrations of sugars, which may also be detected by T1R3 alone.

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

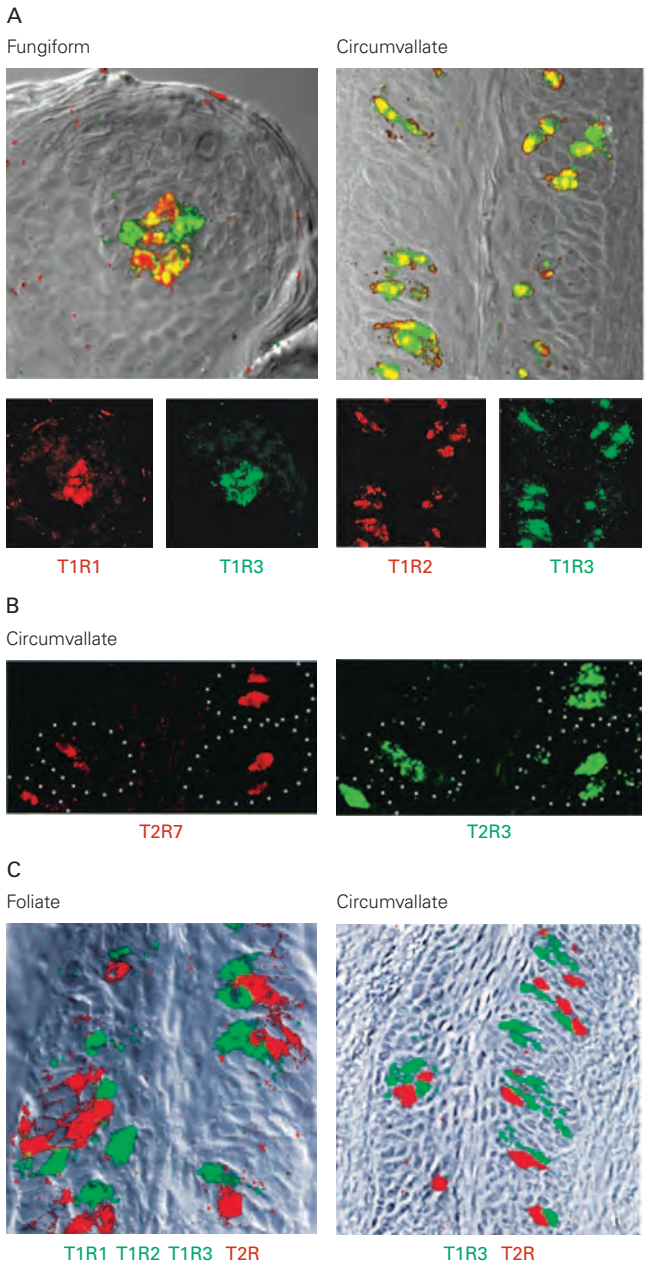

Figure 29–16 (Right) Expression of T1R and T2R receptors on the tongue. Sections of mouse or rat tongue were hybridized to probes that label T1R or T2R mRNAs to detect their sites of expression in taste cells.

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.)