absent in 70%. Biopsy and autopsy investigations have failed to identify neurons in the adult human VNO or the presence of vomeronasal nerve bundles by using a wide variety of neural markers (*56*). Moreover, antibodies against the olfactory marker protein (OMP) have failed to reveal OMP-expressing cells in the human VNO, a finding supported by the absence of an AOB in humans (*57*). The overwhelming evidence would therefore not support a human VNO that is functional in any meaningful way.

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REVIEW

Olfactory Reception in Invertebrates

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Recent progress in understanding the principles and mechanisms in olfaction is the result of multidisciplinary research efforts that explored chemosensation by using a variety of model organisms. Studies on invertebrates, notably nematodes, insects, and crustaceans, to which diverse experimental approaches can be applied, have greatly helped elucidate various aspects of olfactory signaling. From the converging results of genetic, molecular, and physiological studies, a common set of chemosensory mechanisms emerges. Recognition and discrimination of odorants as well as chemo-electrical transduction and processing of olfactory signals appear to be mediated by fundamentally similar mechanisms in phylogenetically diverse animals. The common challenge of organisms to decipher the world of odors was apparently met by a phylogenetically conserved strategy. Thus, comparative studies should continue to provide important contributions toward an understanding of the sense of smell.

Animals can recognize and discriminate chemical signals in the environment, which provide essential information for survival and profoundly influence their behavior. Chemical cues are not only necessary to detect and assess food, mating partners, prey, and predators, but also for communication with other animals. Remarkable chemosensory abilities have been demonstrated in invertebrates, and in many ways, they offer ideal models for addressing basic questions of molecular recognition, chemo-electrical transduction, and processing of olfactory signals. Because most invertebrates rely on olfaction as the principal sensory modality, their olfactory systems have evolved to a level of extreme sensitivity and specificity (*1*). This enables them to identify minute concentrations of behaviorally relevant compounds. The detection of pheromones by the antennae of male moths is a prime example (*2*). Exploring the organization, development, and function of invertebrate olfactory sensory systems may help unravel fundamental principles of chemosensation and contribute to understanding of the more complex process of olfaction in higher organisms. Although invertebrate chemosensory systems display tremendous diversity across phyla, strong morphological similarities are found at the cellular level (*3*). In all olfactory systems, even in animals as phylogenetically diverse as flies, lobsters, or nematodes, specialized bipolar sensory neurons are employed for the detection of odorous compounds. The neurons extend a thin dendrite to the environmental interface and

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project an axon directly toward higher processing centers. The dendrite of the cells terminates in a ciliary structure, presumed to be the site of signal recognition and chemoelectrical transduction.

Receptors for Odorants

The recognition and conversion of olfactory stimuli begins with the interaction of odor molecules with odorant receptors residing on the dendritic membrane of an olfactory sensory neuron. The molecular identity of such olfactory receptors was first unraveled in vertebrates, where a large family of heterotrimeric GTP–binding protein (or G protein)–coupled receptors is involved in the recognition of odor signals. Olfactory receptor genes have been discovered in several vertebrate species, including rats (*4*), mice (*5*), fish (*6*), frogs (*7*), and humans (*8*). In mammals, as many as 1000 odorant receptor types are considered to be employed in olfactory discrimination. Corresponding chemosensory receptors in invertebrates have only recently been discovered in *Caenorhabditis elegans* (*9, 10*) and *Drosophila melanogaster* (*11, 12*).

From direct sequencing of the *C. elegans* genome, more than 500 genes encoding putative G protein–coupled chemoreceptors have been identified (*13*). The majority of genes examined so far are primarily or exclusively expressed in chemosensory neurons. However, a sizable fraction of genes appear strongly expressed either in more than one chemosensory neuron or in some cells that are not chemosensory. Interestingly, multiple chemoreceptor genes are expressed in an individual neuron (*9*). This may allow the cell to recognize diverse odorants and enable the organism to respond appropriately to a large number of chemical stimuli, despite having a relatively limited number of chemosensory neurons. Explicit evidence for an olfactory role has been documented only for the ODR-10 receptor, which is highly expressed in AWA sensory neurons, one of the three types of cells that recognize volatile compounds (*10*). Worms in which the AWA neurons have been killed by laser beams exhibit deficits in the detection of the odorants diacetyl and pyrazine. A more specific loss of chemoattraction, specifically for diacetyl, is observed in mutants that are defective in the *odr-10* gene or the gene encoding a transcription factor (*odr-7*) that controls the expression of ODR-10 in AWA neurons. Expressing the *odr-10* gene in *odr-7* mutants under the control of another transcription factor restored the response to diacetyl. Thus, the presence of the ODR-10 protein is necessary and sufficient for a behavioral response of the worm (*10*). However, the nature of the behavioral response to an odor appears not to be defined by the receptor itself, because expressing the *odr-10* gene in another cell type (AWB) changed the behavioral response to diacetyl from attraction to repulsion (*14*). This provides an elegant demonstration that the behavioral reaction of an organism to an odor stimulus is an intrinsic property of the responding sensory neuron and its integration in a specific neuronal circuit.

The discovery of olfactory receptor genes in the nematode *C. elegans* and various mammals triggered the search for their insect counterparts, mainly by homology-based approaches, but success remained elusive. A breakthrough was finally achieved by searching the *Drosophila* genome database for genes that code for proteins structurally related to known olfactory receptors. Two groups independently reported the discovery of genes, which may encode putative odor receptors of *Drosophila*. Using a novel multivariable computer algorithm, Clyne *et al.* (*11*) first discovered two candidate genes encoding putative seven transmembrane domain receptors, which are specifically expressed in a subpopulation of chemosensory cells. Independently, Vosshall *et al.* (*12*) found a putative olfactory receptor gene by a differential cloning strategy designed to identify rare messenger RNA expressed only in olfactory organs, specifically the antenna and the maxillary palp. Using homology searches in the archives of the *Drosophila* genomic database, a total of 17 related sequences were found by the two groups. Interestingly, the candidate odor receptors of *Drosophila* form a highly divergent family with little sequence identity among their members and no sequence similarity to olfactory receptors from nematodes, vertebrates, or any other family of G protein–coupled receptors. This explains the earlier lack of success in cloning these genes by homology-based approaches. It is not clear why olfactory receptors of vertebrates, flies, and worms share so little sequence identity across different phyla. However, completely independent families of olfactory receptors are also expressed in the main olfactory system and the vomeronasal organ of mammals (*15*). The observed disparity of odor receptors is in strong contrast to other families of G protein–coupled receptors (for example opsins or neurotransmitter receptors), where structure function relationships can be traced over 500 million years of evolution (*16*).

In situ hybridization studies have verified exclusive expression of the members of the *Drosphila* olfactory receptor gene family in some of the ~1200 primary olfactory neurons of the antennae or in the ~120 chemosensory cells in the maxillary palp, or in both types of cells. Interestingly, distinct receptors are expressed in topographically defined subpopulations of cells, and the spatial expression pattern of a given receptor is very similar across individuals (*12*). On the basis of the observation that no co-expression of receptor genes in individual neurons was detected (*12*) and by relating the total number of sensory neurons to the estimated number of receptor genes in the genome and the number of cells expressing a defined receptor, it has been postulated that each individual sensory neuron has only a few receptor types (or at the extreme only one receptor) (*11, 12*). However, the present data are insufficient to establish conclusively the number of receptor types expressed per cell. A more rigorous examination of the kind undertaken recently for mouse sensory cells (*17*) is needed to assess whether receptor gene expression in *Drosophila* resembles either the situation in vertebrates, where an individual sensory cell is believed to be endowed with only one or a small number of odorant receptors (*5, 17, 18*), or the situation in the nematode *C. elegans*, where multiple receptor genes are expressed in one chemosensory cell (*9*).

Little is known about the mechanisms that control the number of receptor genes expressed in an individual olfactory neuron and the specific details of activation of a particular receptor gene from the large variety of receptor encoding sequences present in the genome. Revealing these underlying processes, however, is essential for understanding the basis of odor specificities in olfactory sensory neurons, because the expression of a different pattern of receptor types in each sensory cell presumably determines its ability to respond differentially to odorant stimuli. The finding that in *Drosophila* the POU-domain transcription factor Acj6 governs the chemosensory identity of antennal cells (*19*), may be a first step toward an understanding of the complex regulation underlying the expression of odorant receptor genes. Analysis of *acj6* mutants revealed that the proper expression of a specific subset of olfactory receptor genes relies on Acj6 and the odor specificity of a subset of olfactory neurons is governed at least in part by the action of this transcription factor on odorant receptor genes.

The recent finding of candidate odor receptors in *Drosophila* is also of particular interest regarding a possible relationship between odor receptors and odorant-binding proteins (OBPs). OBPs have been studied in great detail in recent decades, and now after putative odor receptors have been cloned, it may be possible to examine interactions between these two distinct types of proteins. The discovery of abundant, small globular proteins, which bind odorous compounds, in the sensillum lymph of insects (*20*) and the nasal mucus of mammals (*21*) has led to the concept that OBPs may enhance the capture rate of volatile odor molecules by mediating the partitioning of hydrophobic odorants in the aqueous environment which surrounds the dendrites of sensory neurons. The acquisition of OBPs is supposed to be one of the molecular adaptations to a terrestrial life-style which apparently evolved independently in insects and vertebrates, as suggested by the lack of sequence homology (*22*). To date, the identification of various insect OBP subtypes in

moths and in *Drosophila*, as well as evidence for their selective expression in morphologically and functionally distinct sensilla types (*23*), suggests that they are not merely passive transporters of hydrophobic compounds but rather may interact preferentially with specific odorant molecules, thereby acting as selective signal filters or even as co-initiators of the signal transduction process (*24*). In fact, ligand-binding studies have demonstrated different affinities of two pheromone-binding proteins to two pheromone components (*25*), and severe deficits in odor discrimination caused by a defective OBP have been reported for the *Drosophila lush* mutant (*26*). Individual *Drosophila* OBPs and olfactory receptor subtypes show a spatial, overlapping expression pattern. It will be of interest to establish their relationship in more detail, which may provide new insights in how perireceptor and receptor events act in odor discrimination.

Chemo-Electrical Signal Transduction

Chemosensory neurons convert the information about the quality, strength, and duration of adequate chemical stimuli into electrical responses, which are propagated as action potentials along the axon toward higher processing centers, where characteristic physiological or behavioral responses are generated. Biochemical, electrophysiological, and molecular genetic research in phylogentically diverse animals indicates that the fundamental principles of chemo-electrical signal transduction are shared across animal phyla and that similar molecules are involved in olfactory signaling pathways (*1, 3, 27*). The interaction of odor molecules with olfactory receptors on the surface of sensory neurons triggers intracellular G protein–coupled reaction cascades. The receptor-mediated activation of G proteins in turn activates key enzymes of the second messenger cascades. Adenylyl cyclase catalyzes the formation of cyclic 3′,5′-adenosine monophosphate (cAMP) from adenosine 5′-triphosphate, whereas phospholipase C (PLC) hydrolyzes membrane phosphatidylinositol, liberating inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). The rapid increase in the concentration of intracellular mediators activates ion channels in the plasma membrane, thereby generating a receptor potential (Fig. 1).

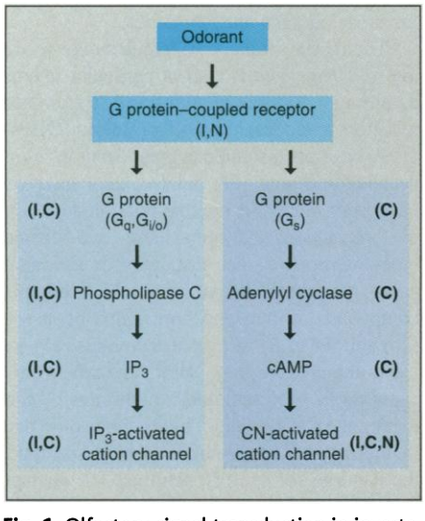

Fig. 1. Olfactory signal transduction in invertebrates. Elements of G protein–coupled signaling cascades are characterized in insects (**I**), crustaceans (**C**) (lobster), and nematodes (**N**) (*C. elegans*). CN, cyclic nucleotide. G_q, $G_{i/o}$, and G_s are specific G protein subtypes.

The involvement of intracellular reaction cascades in the chemo-electrical signal transduction process is firmly established in vertebrates, where the cAMP pathway and the IP_3 cascade appear to operate as two alternative pathways (*28*). Similar second-messenger pathways are also active in olfactory signaling in invertebrates. In particular, the pathways involved in chemosensory signal transduction in lobster olfactory neurons have been studied in great detail and are partially reminiscent of transduction mechanisms in vertebrates (*3*). In lobster, individual odors rapidly and transiently elicit the formation of cAMP and IP_3 in outer dendrites of olfactory receptor cells (*29*). The cAMP pathway results in the activation of potassium channels and hyperpolarization of the cell (*30*), whereas the IP_3 pathway opens cation channels leading to depolarization of an olfactory neuron (*31*). The finding of two second-messenger pathways in lobster, which are linked directly to opposing outputs, was supplemented by cell-free patch-clamp analysis of outer dendritic membranes, demonstrating that cyclic nucleotide– and IP_3-gated ion channels can occur in the same cell (*32*). It has been proposed that chemosensory information is not only transduced but also processed on the level of the sensory cell. Natural odors are usually complex blends of chemicals. They probably activate both second-messenger systems and opposing membrane conductances in an individual neuron; thus, a sensory cell indeed would function as a complex integrating unit. Different odorants elicit opposing responses in individual lobster olfactory neurons (*32*). This implies more than one receptor type in these cells and supports the notion that this may be the case for invertebrates in general, as shown explicitly for *C. elegans* (*9*).

In insects, the mechanisms of signal transduction are less clear. However, the recent discovery of genes encoding putative G protein–coupled olfactory receptor proteins in *Drosophila* agrees with biochemical and molecular genetic data, suggesting that G protein–mediated reaction cascades, notably the IP_3 pathway, are active in olfactory signaling. Initial evidence for the IP_3 pathway came from studies on insect antennal preparations, which demonstrated a stimulation of PLC by odorants and pheromones (*33*). An involvement of PLC in odor perception is also indicated by impaired olfaction in *Drosophila norpA* mutants, suggesting that odorant responses require an intact *norpA* (PLC) gene (*34*). For a variety of insect species, stimulation of antennal preparations with sex pheromones elicits an increase in the IP_3 level in a species-, tissue-, and sex-specific manner (*33, 35*). The odor-induced IP_3 signal shows a rapid and transient time-course that is physiologically relevant (subsecond timescale) (*36*), matching the phasic electrical response of the olfactory receptor cells. The stimulatory effect of pheromones and odorants is dependent on guanine nucleotides; however, the identity of the one or more G proteins that couple odorant receptors to IP_3 formation is still unsolved, although alpha subunits of G_o and G_q proteins have been identified in antennal tissue of a variety of insects (*37*). Also, how the IP_3 signal elicits an electrical response of the sensory neuron is not clear; so far, IP_3-induced currents mediated by distinct cation channels in the plasma membrane have been recorded from olfactory neurons of different insect species (*38*). The cAMP pathway may also play a role in insect olfaction, because cyclic nucleotide–sensitive channels are expressed in the antennae (*39*) and are required for the proper transduction of subsets of odorants (*40*). Although their presumptive role in olfactory signal transduction is not yet explored, the discovery of cyclic nucleotide–sensitive channels suggests the existence of dual transduction pathways in insects.

Evidence for two distinct pathways of olfactory signal tranduction emerges also from recent analysis of chemosensory mutants of *C. elegans*. Mutations in the *tax-2* and *tax-4* genes, encoding subunits of cyclic nucleotide–gated channels, selectively prevent the animal's response to distinct odorants (*41*). Similarily, *osm-9* mutants, defective in a protein related to transient receptor potential (TRP) channels active in the PLC-mediated phototransduction of *Drosophila*, show selective defects in chemotaxis (*42*). Thus, in *C. elegans* two different types of ion channels appear to mediate the electrical responses of chemosensory cells. The nature of the second-messenger systems activating the channels is largely unclear. It has been proposed, on the basis of the similarity of the *osm-9* gene product and the *Drosophila* TRP phototransduction channels, that a similar G protein–mediated pathway involving PLC, IP_3, and diacylglycerol, as used for the control of TRP channels in photoreceptor cells, plays a role in chemosensory cells expressing the OSM-9 channel. Cyclic GMP may play a functional role in activation of the TAX-2/TAX-4 cyclic nucleotide channel. The *C. elegans* genome contains at least 29 genes that encode guanylyl cyclases; some of them are expressed in specific subsets of sensory neurons and some membrane-bound isoforms may function as primary sensory receptors (*43*). The *daf-11*

gene encodes a guanylyl cyclase isoform similar to the enzyme controlling the cGMP level in vertebrate photoreceptor cells and is required for normal chemotaxis mediated by the ASE and AWC sensory neurons. Because a mutation in the *daf-11* gene causes a similar phenotype as in *C. elegans tax-2/tax-4* mutants defective in the expression of the cyclic nucleotide channel in AWC neurons (*44*), it has been suggested that a guanylyl cyclase–mediated modulation of the cGMP levels might act on the TAX-2/TAX-4 channel.

Conclusions

Cross-phyletic comparisons have revealed striking similarities concerning the organization of olfactory systems as well as the physiological principles and molecular elements underlying the process of chemical sensing. The existence of phylogenetically conserved strategies for detection and discrimination of a vast array of odorants seems to reflect the evolutionary answer to the common challenge imposed by the nature of these chemosensory stimuli. Thus, considering the evolutionary conservation of chemosensitivity, comparative studies using the advantage of invertebrate model organisms should continue to help elucidate fundamental mechanisms of olfaction.

The recent progress in unraveling the molecular machinery mediating the chemo-electrical transduction process in nematodes and arthropods, and in particular the discovery of odor receptors in invertebrates, opens new experimental avenues for deploying the advanced genetic tool kits available in *C. elegans* and *Drosophila melanogaster*. These advances may also initiate studies of olfaction in insect species which damage crops or transmit human diseases. These insects depend heavily on the sense of smell to find food and mates. Detailed knowledge of the relevant receptor types and transduction elements would facilitate the efforts to find compounds that interfere with the insect olfaction and may eventually allow control of insect pests without employing neurotoxic compounds. Thus, research efforts in the field of invertebrate olfaction not only provide greater insight into the fundamental principles of how organisms decipher the world of odors, but also have important ecological and economical potentials.

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REVIEW

A Systems Perspective on Early Olfactory Coding

Gilles Laurent

This review critically examines neuronal coding strategies and how they might apply to olfactory processing. Basic notions such as identity, spatial, temporal, and correlation codes are defined and different perspectives are brought to the study of neural codes. Odors as physical stimuli and their processing by the early olfactory system, one or two synapses away from the receptors, are discussed. Finally, the concept of lateral inhibition, as usually understood and applied to odor coding by mitral (or equivalent) cells, is challenged and extended to a broader context, possibly more appropriate for olfactory processing.

The recent wealth of behavioral (*1–3*), genetic (*4*), molecular (*4–7*), physiological (*8–10*), mapping (*11–16*), and theoretical (*17*) studies on the olfactory system makes olfactory research a most dynamic area in modern neuroscience. This mix of scientific cultures has, however, also produced a sometimes confusing picture of what olfactory coding is about. The relevance for coding of neural placement and neural identity, for example, often is intermixed (*18*), and the methods used to estimate neural responses are so varied that a synthesis of all available data is sometimes difficult. Basic concepts useful to study olfactory coding are thus first briefly reviewed.

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