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Chemoelectrical signal transduction in olfactory sensory neurons of air-breathing vertebrates

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Abstract. When odorants bind to the sensory cilia of olfactory sensory neurons, the cells respond with an electrical output signal, typically a short train of action potentials. This review describes the present state of knowledge about the olfactory signal transduction process. In the last decade, a set of transduction molecules has been identified which help to explain many aspects of the sensory response. Odor-induced second-messenger production, activation of transduction channels, the central role of the ciliary Ca^{2+} concentration, as well as mechanisms that mediate adaptation, are all qualitatively understood on the basis of a consistent scheme for chemoelectrical transduction. This scheme, although necessarily incomplete, can serve as a working model for further experimentation which may reveal kinetical aspects of signal transduction processes in olfactory sensory neurons.

Key words. Olfaction; chemoreception; sensory physiology; signal transduction; receptor current; cyclic nucleotide-gated channel; chloride channel.

Introduction

Since David Ottoson's investigations of chemoelectrical transduction in the olfactory epithelium (OE) of vertebrates [1, 2], a concerted effort by scientists of various disciplines has yielded some insight into the ultrastructure of olfactory sensory neurons (OSNs), the molecular basis of odor detection and the biochemical regulation mechanisms operating in these cells. With the currently available data, a signal-transduction scheme has been constructed that integrates most of what is known about OSNs and explains the generation of receptor current, electrical excitation, as well as adaptation and recovery. In this brief review, I describe the interplay of the main molecular components that lead from activation of odorant-receptor proteins to excitation of OSNs in air-breathing vertebrates. The transduction process is located in the sensory cilia, which detect the presence of odorants in the inhaled air and generate a receptor current that depolarizes the OSN. A sketch of the ciliary transduction pathways (fig. 1) illustrates the interrelations of transduction molecules discussed in the text.

Odorants induce synthesis of cAMP

Adenosine 3,5-cyclic monophosphate (cAMP) was first proposed as second messenger in olfactory signal transduction when it was found to induce electrical signals in the OE (recorded as electro-olfactogram, EOG) and to interfere with odor-induced EOG signals [3,4]. Subsequently, membrane-permeable cAMP analogues, as well as forskolin (a drug that stimulates cAMP synthesis) and isobutyl methylxanthine (a compound that inhibits degradation of cAMP) were found to induce electrical excitation of OSNs when applied to frog sensory cilia [5]. OSNs do not exhibit any selectivity in these experiments: *Every* neuron is excited by cAMP, suggesting that cAMP mediates signal transduction in *All* olfactory neurons, irrespective of odor selectivity. In membrane preparations containing isolated rat or frog sensory cilia, odorants induce cAMP synthesis, a process that depends on a GTP-binding protein [6, 7].

A key role in this process plays G_{olf}, a stimulatory GTP-binding protein α subunit that shows 88% amino acid identity with $G_s\alpha$ [8] and a high degree of sequence identity among species (99% between rat and human, [9]). G_{olf} is abundantly expressed in the sensory cilia of mature

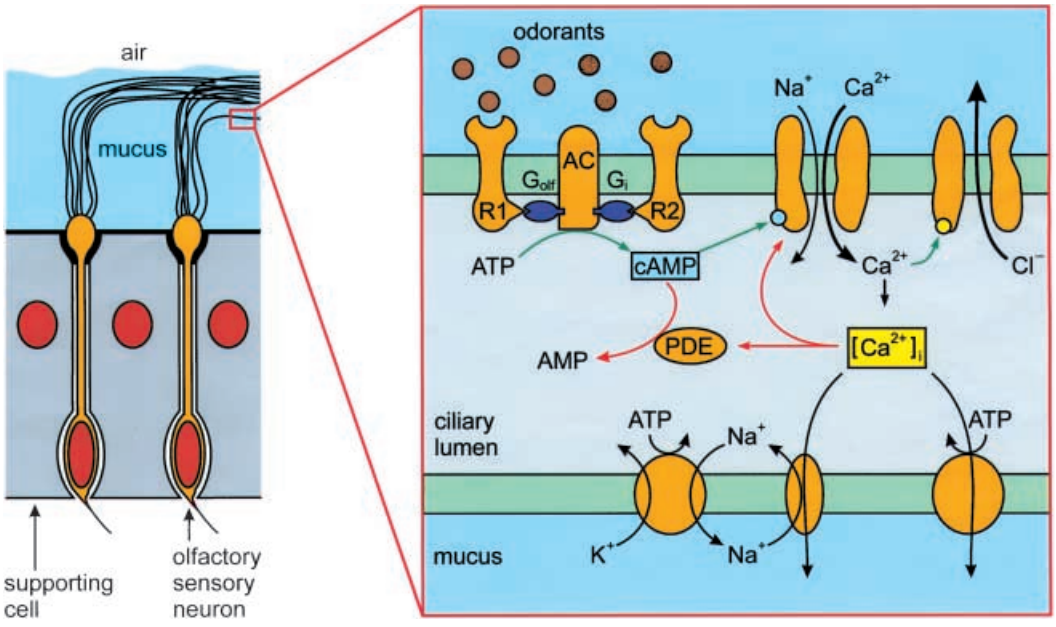

Figure 1. *(Left):* Position of olfactory sensory neurons and epithelial supporting cells in the olfactory neuroepithelium. The chemosensory cilia protrude from the dendritic endings into a layer of mucus and are arranged in parallel to the apical surface. Not shown are microvilli of supporting cells, which rise from the apical membrane to the mucus/air interface [35]. *(Right):* Schematic representation of the cAMP-mediated transduction pathway operating in the sensory cilia. Generation of the receptor current is indicated by green arrows, termination by red arrows. Details are explained in the text. AC, adenylyl cyclase; G_{olf}/G_i, GTP-binding proteins; PDE, phosphodiesterase; R1/R2, odorant receptor proteins.

OSNs [10, 11]. It is activated by picomolar concentrations of odorants [12], and odorant-induced cAMP synthesis can be suppressed by antibodies directed against G_{olf} [12, 13]. Most important, homozygous null-mutant mice that do not express G_{olf} are anosmic to all odorants tested [14], strongly suggesting that G_{olf} is absolutely necessary for olfactory signal transduction. No molecular identification of β and γ subunits of olfactory GTP-binding proteins has yet been reported for mammals and amphibia, but immunocytochemical data show expression of both subunits in rat sensory cilia [15, 16].

G_{olf} transmits the olfactory signal from odorant receptors to adenylyl cyclase which synthesizes cAMP from ATP. The enzyme expressed in the cilia of OSNs belongs to the AC III type of adenylyl cyclases [17, 18]. The protein has an apparent molecular size of ~129 kDa (~200 kDa when fully glycosylated [18]) and is expressed in sensory cilia at an extremely high molar concentration (~100-fold higher than in myocard [17]). AC-III activity is sensitive to Ca^{2+}/calmodulin in vitro [19], however, the extent of Ca^{2+} regulation in intact OSNs is not clear. Ca^{2+} was reported to stimulate olfactory AC III at low (<10 μM [19–22]) but to inhibit the enzyme at higher concentrations [21, 22]. Recent evidence suggests that AC III may be inhibited by Ca^{2+}-binding proteins and by protein phosphorylation (see below). Odorant stimulation of AC-III has been demonstrated in preparations enriched in apical membranes from frog or rat OE, which contain sensory cilia as well as microvilli of supporting cells [6, 22–25]. A consistent observation in these studies is that different odorants stimulate cAMP synthesis with different potency: some compounds are very effective, others show reduced efficacy and some show no detectable effect. A straightforward explanation for this result is that each odorant stimulates cilia derived from a specific subset of OSNs, and that the numbers of cells belonging to each subset differ. This notion is in line with the concept that each type of receptor protein is expressed in only a small subpopulation of OSNs. Accordingly, electro-ol-

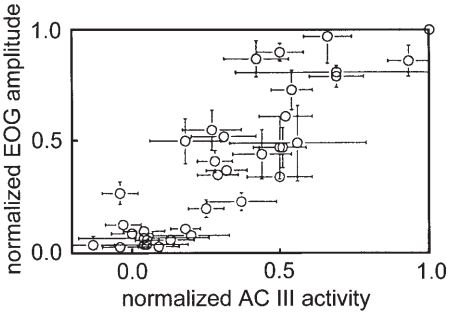

Figure 2. Relation between EOG amplitude measured in bullfrog olfactory epithelium and odor-induced adenylyl cyclase activity in preparations of apical membranes from bullfrog olfactory epithelium. Data for 36 different odorants were normalized to the response elicited by 2-hexylpyridine, the most effective odorant tested in this preparation. The plot shows a clear correlation between the electrical response of the olfactory epithelium and the activity of adenylyl cyclase (correlation coefficient, 0.86; reprinted from [26] with permission of Dr Geoffrey Gold).

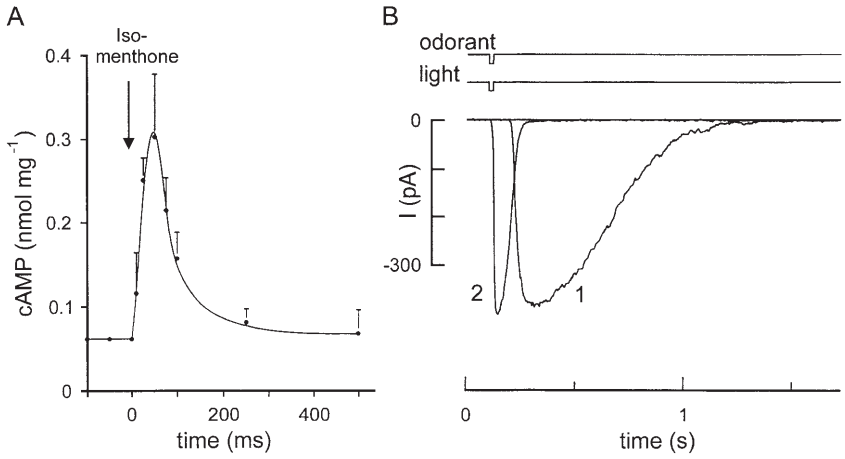

Figure 3. (*A*) Kinetics of cAMP accumulation in an apical membrane preparation enriched in sensory cilia from rat olfactory epithelium upon stimulation with 1 µM isomenthone. The odorant was applied for the indicated duration, and the reaction was stopped using a rapid-quench system (reprinted from [27] with permission of *Nature*). (*B*) (*Trace 1*): Receptor current at –50 mV induced in an isolated rat olfactory sensory neuron by an odorant stimulus of 40 ms duration. The current starts with a delay of 195 ms and declines within 1 s to baseline. (*Trace 2*): Direct activation of CNG channels in the same cell by photorelease of cAMP following a light flash. The light intensity was adjusted to produce a current amplitude similar to the odorant response. The rapid rise and decline of the photolysis-induced current show that the gating kinetics of transduction channels do not determine the time course of receptor currents. This time course probably reflects the concentrations of the messengers cAMP and Ca^{2+} (reprinted from [28] with permission of *Nature*).

factogram (EOG) measurements, which are compound recordings from large numbers of OSNs, show differences in response intensity that are consistent with the biochemical data. Figure 2 shows that EOG amplitude and AC-III activity are closely related [26], a strong indication (i) that the electrical response of the OE to odorants results from AC-III activity, and (ii) that cAMP synthesis observed in the membrane preparations results from activation of sensory cilia.

If cAMP acts as a second messenger, it must be produced rapidly upon odor stimulation. Figures 3 A and B compare the time course of odor-induced cAMP accumulation in a membrane preparation from rat OE [27] to the rise of the receptor current in an isolated rat OSN [28]. Maximal cAMP accumulation is observed after roughly 100 ms in the membrane preparation, whereas the receptor current takes several hundred ms to develop. This suggests that cAMP synthesis is sufficiently fast to generate the receptor current. In intact OSNs, the ciliary cAMP concentration must reach a threshold level to activate the receptor current (see below). The time necessary to accumulate a superthreshold cAMP concentration causes the latency between stimulus and onset of receptor current seen in figure 3 B [29]. The rapid decline of cAMP content during prolonged application of odorants observed in the biochemical assay (fig. 3 A) has not been demonstrated in intact cells, where receptor currents can be sustained for several seconds by elevated levels of cAMP during extended stimulation (fig. 3 B) [28, 30].

Although the role of the stimulatory protein G_{olf} is well investigated, little is known about participation of inhibitory GTP-binding proteins in olfactory signal transduction. Rat sensory cilia appear to specifically express the isoform $G_{i2}\alpha$ in a subpopulation of OSNs [16]. Adding a polyclonal antiserum against an N-terminal domain of $G_i\alpha$ to membrane preparations of rat sensory cilia potentiates stimulation of AC III by odorants [13], which suggests a relief of inhibitory control over AC-III activity. However, an antiserum against the C-terminus of $G_i\alpha$ does not affect the odorant response in the same preparation [12]. Thus, inhibitory input to cAMP synthesis may be restricted to a subset of OSNs, and its physiological role remains to be established.

cAMP opens Ca^{2+}-permeable ion channels

The odor-induced rise of the ciliary cAMP concentration causes activation of cyclic nucleotide-gated (CNG) channels in the ciliary membrane. Estimates of channel density range from 70 μm^{-2} to 1700 μm^{-2} [31, 32], and channel expression was shown over the entire extent of the OSN apical membrane, from dendritic knob to the tip of the cilia [33–36]. Ultrastructural immunocytochemistry has revealed that channel expression is particularly prominent in the elongated distal parts of the cilia [35, 36]. The channels open upon binding of cAMP [34, 37, 38] and are an essential requisite of signal transduction, as homozygous null-mutant mice which lack functional cAMP-gated channels are anosmic [39]. In rat OSNs, CNG channels consist of three distinct subunits (fig. 4 A) that probably form a tetrameric protein complex [40–46]. The cAMP concentration for half-maximal activation is 2–20 µM in mammals and amphibians, and the open probability is

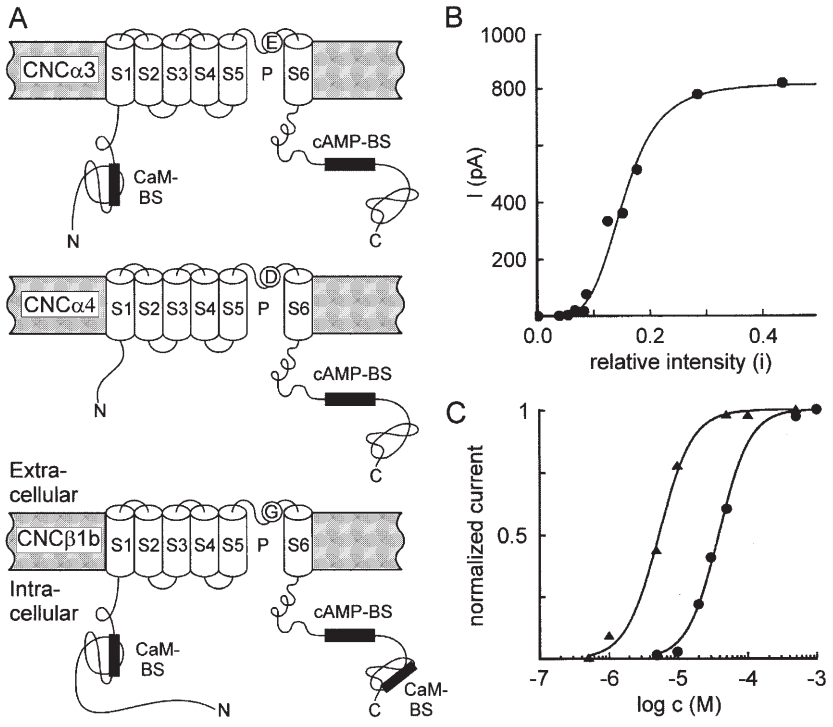

Figure 4. (*A*) Transmembrane topology of the three subunits that form cAMP-gated channels in rat olfactory cilia. CNCα3 is the principal channel subunit, as it forms functional cAMP-gated channels when expressed as homomeric protein. The two modulatory subunits CNCα4 and CNCβ1b determine cAMP sensitivity, ion selectivity, Ca^{2+} permeation and calmodulin-feedback control in the heteromeric channel [44–46]. CaM-BS, binding site for Ca^{2+}/calmodulin; cAMP-BS, binding site for cAMP; P, pore region; S1–S6, transmembrane regions. Note that amino acid residues contributing to the intrapore cation binding site are negatively charged in CNCα3 (E, glutamate) and CNCα4 (D, aspartate), but uncharged in CNCβ1b (G, glycine). (*B*) Amplitudes of current carried by cations and anions across the ciliary membrane at –50 mV as a function of normalized light intensity used to release cAMP from caged cAMP. The relation between the amount of photoreleased cAMP and the light intensity is linear. Consequently, these data illustrate the highly nonlinear dependence of the receptor current on cAMP concentration. The solid line was constructed by a Hill equation, $I = I_{max}\, i^n/(i^n + K^n)$, with I_{max} = 817 pA, K = 0.15 and n = 4.7 (reprinted from [28] with permission of *Nature*). (*C*) Dose-response relations for stimulation by the odorant cineole obtained from two different olfactory sensory neurons isolated from the tiger salamander. A Hill-type equation was fitted to the normalized receptor currents at –55 mV, yielding $K_{1/2}$ values of 5.4 µM and 38 µM, and Hill coefficients of 1.8 and 1.9, respectively (reprinted from [68] with permission of the *Journal of Physiology*).

only weakly affected by membrane voltage [34, 37, 47, 48]. Channel conductance is very low (~0.5 pS) so that each individual channel contributes less than 0.05 pA to the receptor current [49]. Thus, the effects of CNG-channel activation on membrane voltage are limited by low ion conductance. However, extensive biophysical studies of ion permeation have revealed that the channels conduct Ca^{2+} ions from the mucus into the ciliary lumen [50–55], causing a rapid increase of the ciliary Ca^{2+} concentration [56, 57]. Consequently, CNG channels, drive a ciliary Ca^{2+} signal during odor detection that plays a pivotal role in both excitation and adaptation of the OSN.

Ca^{2+}-gated Cl^- channels amplify the receptor current

In addition to CNG channels, the ciliary membrane contains Ca^{2+}-activated Cl^- channels that open upon Ca^{2+} influx [58–61]. Cl^- channels are expressed at a density similar to CNG channels [49]; they have a channel conductance of ~0.5 pS [49] and are half-maximally activated at 5–20 µM Ca^{2+} [58, 61]. Because the Cl^- distribution in the OE favors efflux of Cl^- ions from cilia to mucus (the mucosal Cl^- concentration in rats is ~55 mM [62], and 23–120 mM Cl^- was estimated for the cytosol of rat and amphibian OSNs [62–65]), activation of ciliary Cl^- channels causes a depolarizing inward current. Thus, the receptor current in OSNs has a cationic and an anionic component contributed by CNG channels and Cl^- channels, respectively [66, 67].

Both CNG channels and Cl^- channels show cooperativity in the activation by their respective ligand: the open probability shows a steep dependence on ligand concentration in each channel type, typically increasing from 0.1 to 0.9 within a 10-fold concentration range. The cAMP dependence of the receptor current clearly reflects the cooperative activation of the two contributing channel populations: experiments with rat OSNs have shown that the current across the ciliary membrane rises from 10–90% of its maximal amplitude upon a roughly three-fold step

of cAMP concentration (fig. 4B) [28]. Such a steep dependence on second-messenger concentration is expected to profoundly affect the response characteristics of OSNs. It is probably the reason why individual OSNs show a graded response only within a narrow range of odorant concentrations, spanning little more than a single decade (fig. 4C) [68]. Apparently, the cooperative activation of the two olfactory transduction channels gives rise to a nonlinear amplification mechanism: Fluctuations of cAMP concentration that remain below a threshold value do not induce current, whereas concentrations only a little above threshold cause strong activation. The high signal gain of OSNs (defined as the increment in reponse intensity per increment in odorant concentration) resulting from the cooperative activation of the two transduction channels, may be further augmented by modulation of the ion channels that conduct action currents and control spike generation in the dendro-somatic membrane (see below). These pronounced nonlinear response characteristics suggest that OSNs are designed to produce sensory signals almost in an all-or-nothing fashion within a narrow range of odor concentrations. The wide dynamic range of the whole OE, its ability to discriminate odors at very low as well as at high concentrations, probably reflects the combined activity of many OSNs, each responding to the same odorant with high gain within a different concentration range.

Ca^{2+} and protein kinases terminate the receptor current

Several Ca^{2+}-dependent processes contribute to the termination of the signal and to recovery of the OSN.

1) Ca^{2+} controls the activity of CNG channels by a negative feedback mechanism that reduces the channel's ligand sensitivity [69–72]. The α3 and β1b subunits of CNG channels contain high-affinity calmodulin (CaM) binding sites (fig. 4A) which very effectively control the cAMP sensitivity of the channel. Binding of Ca^{2+}/CaM reduces cAMP sensitivity in rat OSNs, increasing the concentration for half-maximal activation from 3 µM to 60 µM [69]. This loss of cAMP sensitivity develops within 1–3 s after the onset of the stimulus [72], promotes channel closure, rapid termination of the receptor current and fast adaptation to further odor stimuli (fig. 5A, B).

2) The phosphodiesterase isoform PDE1C2 is highly enriched in rat OSNs [73]. This enzyme is activated by Ca^{2+}/CaM and shows a particularly high affinity for cAMP (K_m = 1.2 µM [73]). In unstimulated OSNs, phosphodiesterase (PDE) inhibitors cause electrical excitation [5], indicating that PDE-mediated hydrolysis of cAMP balances the basal activity of AC III. During odor stimulation, cAMP degradation increases at elevated ciliary Ca^{2+} concentrations, thereby limiting activation of CNG channels. During signal termination, PDE restores the basal cAMP level.

3) AC III is phosphorylated by Ca^{2+}/CaM kinase II at elevated ciliary Ca^{2+} concentration [74, 75]. Phosphorylation of Ser^{1076} of AC III in cilia preparations from mouse OSNs attenuates enzyme activity, but the effect of AC-III phosphorylation in intact cells has yet to be demonstrated. Similarly, the Ca^{2+}-binding protein visinin-like protein mediates AC-III inhibition by Ca^{2+} in ciliary membrane preparations [76], but data from intact cells are not yet available.

Evidence from biochemical analysis of odor-induced cAMP synthesis in membrane preparations containing isolated rat sensory cilia suggests an additional mechanism for adaptation: desensitization by phosphorylation of receptor proteins. This process involves the sequential activation of two different protein kinases [77–81]: protein kinase A is activated by cAMP during odor detection and phosphorylates the regulatory protein phosducin, which binds, in its nonphosphorylated form, to G$\beta\gamma$ subunits. Phosphorylation reduces the binding affinity of phosducin and promotes dissociation from G$\beta\gamma$ subunits. This allows a cytosolic receptor-specific kinase (GRK3) to be translocated to the membrane, since the G$\beta\gamma$ subunits function as membrane anchors for GRK3. After membrane translocation, GRK3 phosphorylates activated odorant receptors, uncoupling the receptors from AC III and terminating the synthesis of cAMP.

Taken together, desensitization of CNG channels and cAMP degradation represent robust adaptive mechanisms that rapidly terminate the receptor current in OSNs. In addition, cAMP-synthesis appears to be a target of feedback inhibition, brought about by phosphorylation of odorant receptors and AC III. The exact contributions of the individual processes in vivo, as well as their temporal relations to desensitization and recovery of the OSN, are not yet fully understood.

Ca^{2+} extrusion from the sensory cilia

When OSNs are repetitively stimulated with odor pulses of equal intensity, they exhibit a distinct refractory behavior: the amplitude of receptor currents decreases with the time interval between stimuli (fig. 5A). Similar data are obtained when ciliary CNG channels are directly activated by photorelease of cAMP from caged cAMP (fig. 5B), indicating that adaptation mainly reflects the desensitization of CNG channels at elevated ciliary Ca^{2+} [72]. If two pulses are separated by a time interval of 5–10 s, adaptation is relieved, suggesting that ciliary Ca^{2+} concentration has dropped to levels that allow dissociation of CaM from CNG channels. This relatively fast removal of ciliary Ca^{2+} is mainly achieved by Na^+/Ca^{2+} exchangers

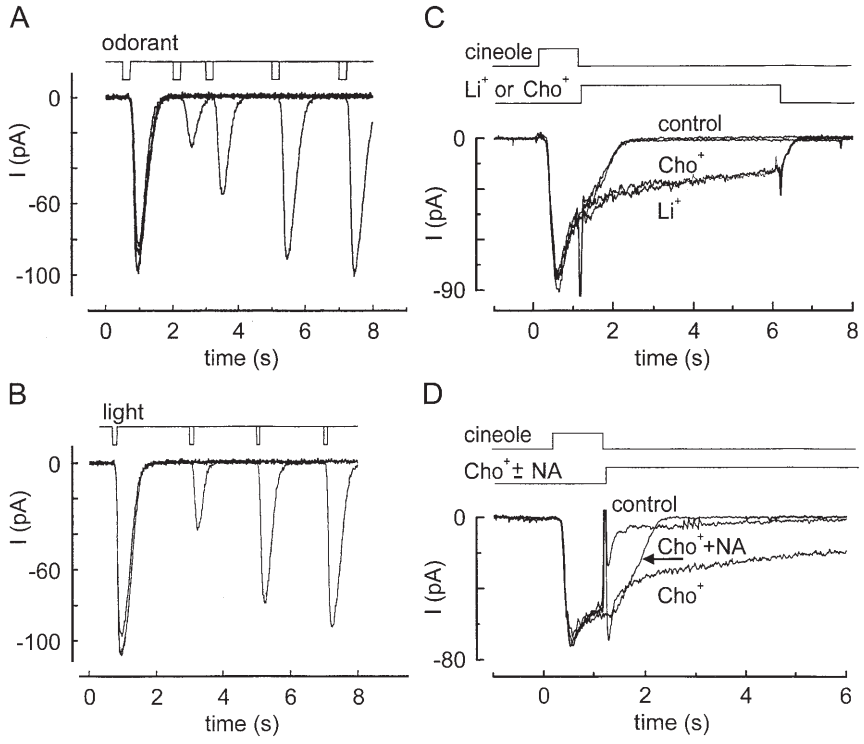

Figure 5. (*A*) Double stimulations with the odorant amyl acetate reveal adaptation of an isolated newt olfactory sensory neuron. Whole-cell currents at −50 mV recorded in four experiments from the same cell. Currents induced by the first of each stimulus pair are superimposed. Intervals between first and second stimuli were 1.5, 2.5, 4.5 and 6.5 s, respectively (reprinted from [72] with permission of *Nature*). (*B*) Refractory behavior in response to photorelease of cAMP. Intervals separating each stimulus pair were 3, 5 and 7 s, respectively. This experiment shows that the adaptive process that causes current reduction during the second stimulation represents a direct effect on CNG channels (reprinted from [72] with permission of *Nature*). (*C*) Na^+/Ca^{2+} exchangers mediate termination of receptor current and recovery from adaptation in frog olfactory sensory neurons. Cells respond to a 1-s stimulation by 100 µM cineole with a receptor current that declines to baseline within 2 s (control). Upon replacing extracellular Na^+ with Li^+ or choline$^+$ immediately after the odor pulse, recovery is strongly inhibited *(Li^+ and Cho^+)*. Neither Li^+ nor choline$^+$ can substitute for Na^+ in the activation of Na^+/Ca^{2+} exchangers. (*D*) The sustained current after inactivating Na^+/Ca^{2+} exchangers *(Cho^+)* is blocked by the Cl^--channel blocker niflumic acid *($Cho^+ + NA$)*. Thus, when Na^+/Ca^{2+} exchangers are inactive, Ca^{2+}-gated Cl^- channels remain open after the odor stimulus because the ciliary Ca^{2+} concentration remains high (reprinted from [84] with permission of the *Journal of General Physiology*).

[82–84] that utilize the electrochemical potential difference of Na^+ across the ciliary membrane to extrude Ca^{2+} from the cilia. This transport mechanism was revealed by demonstrating that the decline of receptor current after the stimulus depends on extracellular Na^+ (fig. 5C). The slowly declining current recorded in Na^+-free solution reflects sustained activity of Ca^{2+}-activated Cl^- channels, as shown by its sensitivity to the Cl^--channel blocker niflumic acid (fig. 5D) [84]. Thus, the activity of Na^+/Ca^{2+} exchangers determines the kinetics of Ca^{2+} clearance from the cilia, terminates the Cl^- component of the receptor current and allows the cell to recover from adaptation. Inflowing Na^+ is recycled by a Na^+/K^+-ATPase which was recently shown to be expressed in rat sensory cilia [85, 86]. An additional pathway for Ca^{2+} extrusion from the cilia may be provided by a Ca^{2+}-ATPase that uses metabolic energy to translocate Ca^{2+} across the ciliary membrane. However, activity of this enzyme has, so far, only been reported for salmon OSNs [87], and no data for mammals or amphibia are available.

Electrical excitation

The resting membrane voltage of OSNs is probably in the range of −90 mV to −60 mV. Because of a very high input resistance (1–20 GΩ), inward currents of only a few pA cause sizable depolarizations and elicit action potentials in isolated OSNs [88]. Inward currents exceeding 10 pA induce trains of action potentials [89], indicating that OSNs respond very sensitively to receptor currents of small amplitude. The depolarization of the ciliary membrane is conducted passively to the dendritic knob and to the membrane of the dendrite. In *Necturus* OSNs, the dendritic membrane is able to generate action potentials [65] and to actively propagate excitation toward the soma. If common to all OSNs, dendritic action potentials represent an important factor for detection efficiency. The somata of OSNs are equipped with a set of voltage-gated Na^+-, K^+- and Ca^{2+} channels that allow repetitive firing of action potentials [90] and even sustained oscillations of membrane voltage with pronounced bursting behavior

[91]. It was recently shown that the action currents in newt OSNs are conducted in almost equal fractions by T-type Ca^{2+} channels and voltage-gated Na^{+} channels [92, 93], and both current types are subject to modulation by adrenaline [94]. Spike generation appears to be mainly controlled by Ca^{2+} channels which activate at more negative voltages and inactivate more slowly than Na^{+} channels. Partial suppression of I_{Ca}, combined with a negative shift of the Na^{+} channel-activation curve, have been observed upon application of adrenaline or activation of protein kinase A. By regulating the channel activity, adrenaline increases the response to current injection, and was suggested to further narrow the dynamic range of odor response in newt OSNs [94]. Voltage-gated channels in OSNs are also modulated by dopamine [95] and gonadotropin-releasing hormone [96], illustrating efferent control of OSN excitability.

Thus, OSNs are electrically compact, respond sensitively to depolarizing currents and are capable of generating bursts of action potentials. An unmyelinated axon transmits the signal to the brain: axons from several OSNs are collected in a nerve fascicle and ensheathed by a single Schwann cell. Axons do not form collaterals and receive no efferent input. They synapse in the olfactory bulb of the brain onto secondary neurons (mitral cells), which integrate the sensory signal and relay the olfactory information to further levels of processing.

Open questions

It appears that the major components of the cAMP-mediated signal transduction pathway in OSNs have been identified. The second level of investigation, the quantitative analysis of their interactions, is only just beginning, and several important points are being addressed:

1) What is the density of each protein species (receptors, G proteins, AC III, ion channels, exchangers, pumps) in the ciliary membrane? How is their spatial distribution across the length of the cilium?

2) What are the concentrations of soluble transduction proteins? Of particular interest are the various Ca^{2+}-binding proteins that have been identified in OSNs [76, 97]. What are their target proteins, and what is their Ca^{2+}-sensitvity?

3) What are the concentrations of the two messengers cAMP and Ca^{2+} during the odor response? How is their spatial distribution within the cilium? What are the threshold concentrations of cAMP and Ca^{2+} for inducing receptor currents? How do concentrations change during adaptation?

4) What is the ionic composition of the receptor current? What are the concentrations of permeant ions in cilia and olfactory mucus? Are there homeostatic mechanisms that control mucosal ion concentrations?

5) How are the precise temporal relations between activation and inactivation of the various enzymes and channels? What determines the time course of amplifying and adaptive processes?

6) Are other signaling mechanisms involved in olfactory signal processing? Several additional transduction pathways have been proposed to be active in OSNs, including the phosphoinositide metabolism [24, 98–100], generation of nitric oxide and carbon monoxide [101–104], and a guanylyl cyclase/cGMP pathway [105–109], but their physiological roles are not yet understood [110].

Thus, kinetic investigations of enzyme reactions, of second-messenger dynamics and of ion transport pathways, as well as ultrastructural studies of olfactory cilia, must be combined to create an integrated model that can explain generation and termination of the receptor current, as well as adaptation and recovery of OSNs. This model will certainly look considerably more complex than figure 1, but will help to understand how chemoelectrical signal transduction works.

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