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Speculations on receptor cells as analyzers and filters

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The contributions to this volume document the rapid increase in knowledge of olfactory neuroscience which has occurred during the past decade and the exciting prospects for future progress. Much has been learned about the cell biology of olfactory neurons and other cells constituting olfactory tissues. The physiological and behavioral roles of chemosensory organs in a variety of organisms have been explored and a rational teleology is emerging. Anatomical and developmental knowledge is in a stage of explosive growth and, as a result, many of the naive assumptions of a decade ago are being discarded. The synthetic capabilities of fragrance chemists have led to what will probably be precise establishment of the chemical basis for perceptual experience. In spite of all this, there are major shortcomings in what we know and understand.

For the chemical senses of all organisms, from bacteria to primates, there are two central questions. 1. How do these senses work? 2. What do they do? Much of this volume addresses the second question. We know less about the first.

Bacterial chemoreception is best understood[30]. The complex chemotactic behavior of *Escherichia coli* has been dissected using genetic mutants. There are separate receptor proteins for each of the many different stimulus substances which can influence movement. Receptor messages are integrated by transducer proteins. These in turn modify the proteins which control the motile flagella. In higher organisms, although comparable mechanisms are postulated, the nature of the receptors on the sensory neurons is not known. Nor is it possible to predict how different receptor cells will differ in their responses to a stimulus or how the resulting differences in cellular activity are processed by the nervous apparatus to direct an orderly change in behavior.

In this chapter a variety of experimental evidence is interpreted to imply that olfactory receptor neurons are more than simple stimulus detectors. The hypothesis is advanced that the unusual morphological features of these cells and tissues are accompanied by biochemical and physiological specializations. These specializations within the sensory neurons serve to maximize signal-to-noise ratios, integrate accumulated stimulus action, and suppress responses which do not carry meaningful olfactory information.

A. Receptor morphology

The somata of the receptor neurons in vertebrates are located in epithelia lining the nasal cavity. Each neuron has a single dendrite which projects to the epithelial surface. It terminates in an olfactory knob from which grow either cilia or microvilli. Proximal to the knob tight junctions connect dendrites to the apical regions of enveloping supporting cells[4]. These junctions form a diffusion barrier which prevents ionic and stimulus substance fluxes between the receptor surface and the rest of the extracellular space of the epithelium. Receptor neuron dendrites lie in separate invaginations in supporting cells[11, 23]. These isolate each neuronal dendrite from its neighbors and (probably) allow rigorous control by the supporting cell of the ionic composition of the fluid surrounding the dendrite. Dendrites are of various lengths and small diameters. The cell bodies from which they grow are large. They are not enveloped by supporting cells. Instead they are jam packed against each other. The dendrites in vertebrates are 1–2 μm in diameter and 20–100 μm long. These long, thin processes expand dramatically in cross-sectional area to form cell somata, typically

5–15 μm in diameter and twice as long, and then again dramatically constrict to form unmyelinated axons 0.1–0.2 μm in diameter. These extremes of cross-sectional area and membrane surface/unit length impose limits on neural transmission processes. In particular, the soma presents a large capacitive load which will make it unlikely that action potentials can invade and which will reduce the rate of any potential change[41].

The relations between axons and their surrounding cells contrast sharply with those of dendrites. Hundreds of naked axons lie in a single invagination of a Schwann cell[8]. When action potentials occur, there will be ion concentration changes which will affect axonal neighbors[10]. There are several such invaginations in each Schwann cell. The olfactory nerve is the only nerve in the body organized in this way.

From the olfactory knob at the distal end of the neuron, cilia or microvilli project into the mucus of the nasal cavity. Amphibia have a few long cilia which are motile during their early developmental life[28, 37, 45]. Mammals have many short cilia which are never motile[35]. Receptors of the vomeronasal organ, whose axons form the accessory olfactory nerve, have microvilli on their distal surfaces[23]. Cilia and microvilli have diameters of 0.1–0.2 μm. The longest cilia (found in *Rana*) are 250 μm long. Mammalian cilia are shorter, typically up to 50 μm. Among vertebrates, regardless of species, the total ciliary surface area per cell is approximately constant[39]. Microvilli have lengths of a few μm. Animals without vomeronasal organs, such as teleosts and some amphibians, have an olfactory epithelium constituted of a mixed population of ciliated and viliated receptor neurons[11]. Recent results support earlier suppositions that the proximal portions of the cilia contain the majority of the effective stimulus transduction sites[3, 21, 22, 43]. This is also a region of high density of membrane surface particles identified by TEM examination of freeze-etched materials[40]. Stimulus transduction sites on the cells with microvilli have not been experimentally localized.

B. Receptor membrane processes

Odorous chemicals can probably affect neuronal receptor membranes in several different ways. A stimulus may act on proteinaceous membrane outer surface receptors which are directly coupled to membrane channel ionophores[18]. Many odorous substances are more soluble in oil than water. These may move from watery mucus into the membrane lipid and find hydrophobic receptor sites on membrane-spanning proteins which are coupled to ionic channels[36]. Alternatively, a second messenger system may intervene between reception and transduction. Lancet has found odorant-stimulated, GTP-dependent cAMP synthesis in olfactory cilia preparations[5, 32, 44]. He postulates a surface odor receptor coupled by membrane-spanning proteins to the intracellular enzyme system which activates membrane conductance changes.

Odors also may act more generally. Kurihara postulates that odors can act by altering the charge on the membrane double layer capacitance and thus alter transmembrane voltage without affecting membrane ionic channels[48]. Finally, lipid soluble stimuli could dissolve in membrane lipid, disorder it, and modify leakage conductance[6]. Several laboratories have preliminary results with membrane reconstitution and patch recording techniques which show that there are ionic channels in chemoreceptor membranes[31]. However, there is no convincing proof that these or any of the other postulated mechanisms are responsible for transduction.

As a fallback position, we might assume that any mechanism which can affect the sensory membrane voltage will probably act under some conditions. In the cases where we postulate specific receptor entities positioned in the membranes of those parts of the neuron exposed to the external environment, the conditions which determine stimulus-response functions are straight forward. Stimulus effectiveness will be determined by the relations between the input impedance of the receptor membrane and the density of odor-sensitive ionophores. The cell input impedance will be high if the number of open non-odor-sensitive channels is low. In this situation a stimulus need open only a few channels to significantly change receptor current and membrane polarization. This cell has high stimulus sensitivity. However, high input impedance results in low signal-to-noise ratio because spontaneous fluctuations in non-odor-sensitive channels are more likely to generate action potentials in the absence of a stimulus.

High input impedance (low channel density) also increases the sensitivity of the membrane to non-specific stimulus effects. Stimuli which disorder lipids or modulate the double layer capacitance will have a strong effect on membrane potential when there are few open ionophores to provide a stabilizing shunt conductance. The few measurements to date of olfactory receptor neuron input impedance suggest that it is one or two orders of magnitude higher than that of most neurons. This means that channel density in those regions of the neural membrane electrotonically close to the cell soma is low[12, 13, 20, 47]. Present data do not allow extrapolation of these results to the transduction region of the cell because there are no data on the length constants of the long, thin dendrite and cilium.

Under the 'anything which can happen probably will' hypothesis, there are two classes of transduction mechanisms. One class consists of processes which are selective, responding to a small set of substances which interact with receptors with high affinities. Analogs of these processes are synaptic transmission and antigen-antibody reactions. It is assumed that such receptor molecules are not uniformly distributed across the receptor cell population and that any particular stimulus affects some cells more than others. The other class includes those processes with low selectivity. These include chemical stimuli which disorder the ciliary membrane, resulting in leakage conductivity changes, and those which alter ionic affinities of the membrane surface and thereby the charge on the capacitance of the double layer. These effects depend only upon bulk physical properties such as solubility, dipole moment, and partition coefficient. A wide range of stimulus substances will produce identical effects on a receptor cell if the concentrations are appropriately adjusted. These effects are likely to be identical on all neurons of the receptor epithelium with low open channel density. Since these effects are non-specific they must be

regarded as noise which will have the effect of diminishing olfactory discrimination capability.
We are searching, then, for mechanisms which will result in both high sensitivity and high discriminability, i.e. processes which transmit specific receptor activation and reject non-specific receptor membrane responses.

C. Receptor cell behavior

Intracellular microelectrode records from receptor neurons in vivo and from cells in epithelial preparations have been notoriously difficult and have revealed little about the biophysical basis for transduction and impulse initiation[20, 38, 46, 47]. There are several provocative results. Cell penetrations apparently occur only in the soma region, probably because of the small dendritic and axonal diameters (2 and 0.2 μm, respectively). Most of the time penetration is accompanied by a negative potential shift of 50 mv or less, a few action potentials, the first of which is 70 mv in amplitude with successive ones decreasing in amplitude, a rapid decline in negative membrane potential, and no further activity. In other words, penetration makes the cell leak, evokes a few soma membrane spikes and kills the cell. Sometimes the leak seals and a sustained negative resting potential is recorded. Input impedance measured in this situation is of the order of a gigaohm. Spontaneous axon action potential activity returns after the seal. However spike amplitudes are lower than those in most neurons, as if the electrode recording location in the soma was one or more length constants away from the location of spike generation. Stimulation with odor evokes barely detectable depolarization, as if the site of transduction was also electrotonically far from the position of the recording electrode. This appears to be the worst possible combination of properties that a neuron can possess when its mission is detection of very low concentration stimuli. In spite of this, the nose is a much more sensitive detector of some chemicals than the best analytical instruments.
If the cell membrane conductance is uniform over the cell surface, the observations of high input impedance contradict the observations of spatial signal decrement over distances of the order of 100 μm. The experimental evidence may be faulty due to penetration-induced damage, electrode tip plugging, incomplete reseal, etc. If the soma intracellular records are faithful, then the properties of the cell membrane must be very different in different parts of the cell. The transducer region (probably ciliary membrane) must be separated from the soma by a leaky dendrite which shortens the length constant. The soma membrane must appear to be nearly a pure capacitance, looking to the electrode as a high impedance and looking to the dendrite and axon as a long time constant capacitive load. The axon hillock must be leaky, shortening the apparent length constant of the axon and shunting spike amplitudes recorded in the soma.
This model is not teleologically attractive because of the multiplicity of assumptions. It is not biologically attractive because the shunting dendrite and hillock regions attenuate the receptor current available for axon spike generation. The one saving grace is that it allows the large capacitive load of the presumed low channel density soma to act as an integrator, storing transduction charge to cause a maintained action on impulse generation. It would act as a low pass filter, eliminating input fluctuations and informing the axon of those events which are maintained. It would sum active, all-or-none transduction events in the cilia. The signal transformation would not be obvious in intracellular voltage recordings because most of the signal would consist of axoplasmic currents rather than transmembrane current fluxes (and resulting voltage changes).
There are three possible interpretations of the results of intracellular microelectrode recordings. We can ignore them as mostly artifactual. We can accept them at face value and, using simplistic neural models, conclude that the olfactory receptor neuron is a very inefficient transducer. Or we can postulate a complex, heterogeneous cell surface constructed to preserve signal energy in spite of a geometry which appears to waste it.
If we knew more about the physiological properties of different parts of the cell surface, there would be a basis for choosing among the three interpretations. Extracellular recordings of the field potentials of single receptor neurons contribute some information on this issue. This electrophysiological method is much better than the intracellular one for localizing sites of membrane events[9]. In addition it generally does not cause cell damage and message distortion. De Kramer used it to show that odor reception in the sensilla trichodea of male *Antheraea polyphemus* moths is transmitted by an all-or-none active process in the dendrite[7]. Currents from the dendritic spike traverse the soma and affect the axonal impulse generation process. *Antheraea* sensilla trichodea have several morphological similarities to vertebrate olfactory receptors[29]. The dendrite in the vertebrate and the modified cilium in the moth connect the transduction site to the soma. Both are long and thin. Somata of both cell types are relatively large. A tight junctional region separates the transduction region from the axon impulse generation region. Axons are unmyelinated and of very small diameter.
There is suggestive evidence that transduction events in vertebrate olfactory receptors may also be actively transmitted to the soma rather than by the more common process of passive electrotonic propagation. Some action potentials in rat embryo and frog olfactory receptors have a low-amplitude all-or-none component in the single unit field potential preceding some axon spikes[14, 16]. It has been postulated that this is due to a stimulus-evoked all-or-none event in the dendrite. Spontaneous axon spike potentials do not have this early component.
Accepting electrophysiological results at face value (always dangerous) and postulating that nature has selected for high sensitivity and selectivity lead to the notion that the receptor neuron dendrite and soma constitute an integrator (and low pass filter) which preserves stimulus trends and histories and reduces the noises associated with slamming gates and effervescent channels.

D. Receptor cell development

Explorations of the odor response profiles of olfactory receptor neurons in rats and frogs reveal that there are two classes of neurons[1, 17]. These classes can be separated

on anatomical and developmental grounds. Early in development in the rat embryo, receptor cells are not selective. They respond to most odorous chemicals. As they mature and their axons project to their synaptic targets in the olfactory bulb, they become selective. Only some odors are effective in evoking increases in action potential rate.

In all vertebrates, there is continuous receptor neurogenesis[24]. Neuronal lifetime depends upon the rate of nasal infection (and probably other environmental insult)[26]. In adult frogs newly formed receptors have long dendrites and cilia and axons too short to reach their targets. These cells are like young rat embryo neurons. They are not very odor-selective and have relatively simple action potential parameters[1,3]. Mature neurons, with short dendrites, long cilia, and synaptic connectivity are more sharply selective in their odor responses and appear to have more complex active membrane processes. When the epithelium is treated to cause degeneration, either by section of the olfactory nerve or by zinc sulfate lavage of the nasal cavity, it regenerates. The extent to which physiological processes in regenerating epithelia parallel those in tissues undergoing normal neurogenesis is not resolved[34]. This preparation does allow measurement of changes in stimulus sensitivity of the neuronal population during regeneration. In the regenerating epithelium, stimulus sensitivity as measured by the electro-olfactogram (EOG) at first recovers linearly and at different rates for different odors. At about the time that the epithelium is mostly repopulated with neurons and when some of the axons have grown to reach the olfactory bulb, there are abrupt increases in EOG amplitudes for those substances whose initial recovery rates were low. It is as if there was a burst of incorporation of odor-selective channels following synapse formation.

Our working hypothesis is that newly differentiated neurons have no receptor molecules in their ciliary membranes. The non-selective responses and linearly increasing EOGs result from stimulus disordering of the lipid membrane or change in double layer capacitance and from the increasing receptor membrane area as cells are added and cilia grow. The transition to selectivity and the abrupt return of normal EOG amplitudes are the result of incorporation of receptor molecules and ionophores coupled to them into the ciliary membrane.

We cannot rule out alternative explanations. New cells may have all possible types of receptors, some of which are resorbed at the transition to maturity so that the cells become selective in their responses. The cell surface molecules may be multipotent in their response capabilities and become transformed into selective acceptors either under genetic control or as a result of stimulus exposure. All of the processes for receptor regulation elsewhere in nervous tissues can be postulated to apply to olfactory receptors. The critical experiments have not been done. The evidence available, however, supports the notion that neurons are different in their chemical sensitivities at different times during development. The developmental process appears to improve the capacity of the receptor neurons to discriminate among stimuli and to reduce sensitivity to processes which have common effects across the neuronal population.

E. Receptor neurons as analyzers

There is a curious disparity in reports of maximal spike rates in olfactory receptors. Odor-evoked responses measured in single cells are as high as 100 spikes per second. Stimuli can be repeated time after time and evoke nearly identical responses[15,27]. There is little adaptation in the EOG[42]. However, if the olfactory nerve is stimulated electrically and antidromic spike activity is recorded from single neurons, the results are dramatically different[2,19]. If a shock is delivered once every minute, a neural action potential results only from the first 4 or 5 shocks. After that, the axonal excitability is profoundly depressed. The difference, of course, is that with electrical stimulation all of the nerve fibers are activated synchronously, while with odorous stimulation only a few are active. The anatomical arrangement of olfactory nerve axons provides a logical (but unproven) explanation. Several hundred axons lie in a single invagination in a Schwann cell. Axonal diameters are small and remarkably uniform. An electrical shock will result in synchronously occurring spikes in most of the axons, increased potassium concentration in the extracellular space, and increased intracellular sodium concentration[10]. Until metabolic processes can return these concentrations to normal, excitability will be reduced due to sodium channel inactivation.

The implications of this are clear. When chemical stimulation causes receptor currents in a large proportion of the neural population, only a few spikes per cell will be transmitted to the olfactory bulb. Stimuli which act in non-selective ways by disordering lipids or by changing double layer capacitance will result in only a small increase in glomerular signals. This activity dies out quickly if the stimulus is maintained. An odor which acts selectively on a small proportion of the receptor population will not face reduced axon excitability because most of the axons within a Schwann cell invagination will not be active. Furthermore, activity from a spatially localized population of neurons which are sensitive to the same stimulus will be lower than it would be if the neurons were spatially dispersed.

Thus the olfactory nerve, unique among sensory nerves in its anatomical arrangement, is probably organized to act as an analyzer and filter. It efficiently transmits weak stimuli which activate a small and widely dispersed portion of the receptor population. It responds much less vigorously to stimuli which non-selectively activate neural receptor membrane. Increase in stimulus intensity will have less than a proportionate increase in evoked activity. Spatial localization reduces stimulus discriminability. This modulation of sensitivity as a result of axon bundling postulated here is analogous to lateral inhibitory synaptic organization such as has been so elegantly investigated in the eye of *Limulus*[25]. The primary receptors appear to be capable of enhancing contrast and reducing transmission of stimulus effects with low information content without using interneurons or efferent feedback.

There is evidence for maintained increase in extracellular potassium concentration in the olfactory nerve[10]. None of the other anatomical and physiological studies which could affirm or deny the coding and information transformation mechanisms proposed here have been done.

F. Summary

Speculating on smell is still intriguing[33]. Much is yet to be learned about the olfactory sense.

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