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The biology of olfaction

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The biology of olfaction: An introduction

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Olfaction has come of age as a scientific topic. Lewis Thomas[5] places the olfactory receptor as number five on his list of the seven wonders of the world because it is a genuine neurone exposed to the open air, serving an extraordinary function of chemoreception. Only the uninitiated could describe it as having no real significance for humans, and the present review should help to decrease their numbers.

In recent history several crucial research contributions have been made. One was by Adrian[1], the first researcher who, during the early fifties, was able to record from single units among the second order olfactory neurons in the bulb. The technology at that time did not permit recording from the extremely small neural units in the olfactory mucosa. However, Adrian's data did suggest that there were different types of olfactory receptors and that the olfactory code could be described electrophysiologically. His work greatly encouraged other researchers. The second contribution was made during the latter half of that decade by Ottoson[4] in research closer to the olfactory receptors. He demonstrated the existence of a dc potential at the surface of the olfactory epithelium during stimulation with odorants, and it was described as an electro-olfactogram (EOG). By careful study of the amplitude and time course of this slow negative shift in voltage Ottoson thus studied the locus of olfactory transduction, the effects of stimulus concentration, and the response of the olfactory organ to adaptation. His research established the EOG as an olfactory response and the widely held hypothesis that it represents the summation of generator potentials emanating from a population of olfactory receptor neurons. It entailed a large step closer to the goal of understanding the wonder Thomas describes. Ottoson's contribution was made just before the great increase in support for science, and it spawned a stimulating debate and a very active period of research. The development of methods for recording from various levels of the olfactory system has created a field of chemosensory neuroscience in which one could now begin to observe interactions in the system. At present, in the mid-eighties, olfaction can compete with vision as a model sensory system.

Contemporary olfactory research is well represented by Gesteland and his colleagues[3] who actually first recorded from the single olfactory neuron, a third significant contribution. Two old and important problems can now be studied, and both are treated in detail below. First of all, there is the possibility raised by Adrian that there may be specific receptor types, that is, primary neurons which respond to certain specific chemicals and not to others, analogous to photoreceptors stimulated by certain stimuli from the visual spectrum. Second, one can now study the integration of the neural activity of the neurons in the bulb, and at other levels in the olfactory pathways, and in the brain.

The first problem of receptor types brings one head-on with the crucial problem of the nature of the olfactory stimulus that some chemicals do and some do not smell. What is the difference between them as far as the olfactory receptor is concerned? This is the topic of the first paper of this collection by Ohloff. Many theories or speculations have been offered, but Ohloff suggests a pragmatic approach to overcome the preoccupation with them which has characterized earlier work, and he provides a framework for it.

It is evident that the olfactory system is capable of responding to an enormous number of chemicals, including new creations made by the chemical industry for which it is unlikely that the olfactory system has a predetermined categorization system. How does the olfactory neuron respond to a stimulus? How is its effect transduced into a neural response? It is noteworthy that Ohloff does not describe any so-called primaries, perhaps the most popular topic in the history of olfactory research, an approach which assumes that each neuron is activated by a specific stimulus yielding the sensation of a certain odor quality. According to most such odor classification systems there is presumably a limited number of such primaries but combinations of them make possible the rich variety of experience of quality which is believed to be characteristic of olfaction. To return to the more basic problem of the transduction event in the primary olfactory neurons, Ohloff states that, since Ottoson, this process has been assumed to be a biomolecular process in which the chemical interacts with a complimentary receptor molecule site. Various aspects of this fundamental problem involves several of the next papers.

Kleene's review of olfactory reception begins from the point of view of chemotaxis of bacteria which are likely to provide significant information about the chemosensory transduction process in general. Many of the problems of molecular recognition faced by the vertebrate olfactory system have been solved by single celled organisms, and molecular biologists have described many of the mechanisms involved in chemical stimulation and the effects on physiological and behavioral responses in such simple organisms. Kleene reviews this work and relates it to the study of olfactory transduction in vertebrates.

It is important to note that the nature of this process transcends the individual olfactory neuron, for it has been discovered that in the vertebrate system it may constantly be renewed. This process involves the integration of receptor activity with activity at higher levels, and anatomists are exploring the ways in which the new neurons establish connections with second-order neurons. A related puzzle concerns how the system can function stably over time in face of a constant turnover of receptors. Several papers refer to this topic and it is addressed directly in Gesteland's concluding chapter.

The second-order neurons are located in the bulb from which there are projections to higher centers in the brain. It is apparently in this highly ordered system where the afferent olfactory code interacts with a diversity of efferent fibers carrying information from the brain. Scott's review describes the fine structures and functions of the neurons in the olfactory bulb and the projection from there to areas in the central nervous system. He describes the morphology, neurochemistry, and functions of the central olfactory pathways and his thorough paper reflects the explosion of neuroscientific information. It provides the basis for appreciating the biological significance of odor perception and how it in turn interacts with other perceptions and behaviors.

One may describe the biological use of such information in terms of two general functions. The first is that olfaction is used to evaluate the atmosphere and food stuff. A very important question at this level is whether there are innate mechanisms which signal, without prior experience, which chemicals are toxic and which nutritious. A great deal of evidence indicates that the olfactory system is like a tabula rasa characterized by plasticity in which the meaning of odors are established through environmental experience. Perhaps the major function of olfaction is to store odor experiences and associated events in memory for future use. Data has accumulated recently regarding this plasticity of the olfactory system, a theme now seemingly replacing the one of innate olfactory odor control mechanisms, including the assumption of a universal hedonic scale of odorants.

As a direct consequence, several of the present papers deal with the problem of plasticity from different perspectives. To begin with, the development of the olfactory system and the appearance of odor-guided behaviors is precocious in rodents and marsupials. Mair provides the review of the emergence of odor-guided behavior in the rat pup and the maturation of the neurons in the receptor epithelium and olfactory bulb. Pager discusses contemporary research showing the activity of neurons at various levels in the olfactory system. Her discussion includes obviously important 'naturalistic' odor-guided behaviors and shows how internal processes may influence incoming olfactory stimulation. Olfactory researchers have thus increasingly become able to bridge the gap between olfactory brain mechanisms and behavior. One important consequence of this has been that while historically sensory systems were studied from the point of view of the environmental stimuli which activate them, it is now well established that there are efferent connections 'upstream' which influence the olfactory neuron 'downstream'. This is, of course, directly pertinent to odor memory, a primary function of olfaction in human behavior[2].

The study of so-called pheromones and odor-guided behavior is in the traditional mode of olfactory research and calls attention to innate stimulus mechanisms rather than the plasticity of stimulus-response connections. A pheromone is a very effective odor stimulus emited by one organism and affecting another of the same species. The effect of such odors on interindividual sexual behavior has received most of the popular attention, but odor-guided behavior involves much more than that. O'Connell discusses the literature of pheromones in insects, which first called attention to the concept. While it seemed to be a clear-cut case of stimulus control, the evidence now indicates that the specification of such stimuli is a more complex problem than first believed. On the other hand, it is also true that, as a result of the research O'Connell reviews, more is actually known about stimulus factors, receptor events, and behaviors thus elicited.

Following the research on insect pheromones, there was a virtual explosion in the observations made of odor-guided behaviors in vertebrates. Doty reviews this large literature in mammals, including human behavior and perception. He suggests, as is implicit in many other sections of this review, that not only is the problem of defining the stimulus more complex than first assumed, as noted by O'Connell, but the concept of plasticity has entered this field of research as well because the effect of experience, especially with feeding, has also been found to play a large role in odor-guided behavior.

Most of the research described uses animals as subjects, but the review is intended for those with a general interest in human perception and behavior as exemplified by the first review on the odor stimulus, as well as the last one on in which the Berglunds and Lindvall review the recent work in human psychophysics both in the field and in the clinic. Adding to Ohloff's review, it shows the changes that have taken place regarding the old problem of defining the odor stimulus. Where there was primary concern with 'pure' odors, there is now focus on odors as they occur in natural situations rather than the laboratory. This is akin to a change in auditory psychophysics from pure tones to speech sounds. The review also reminds us

that the problem is a multidisciplinary one, relating chemistry, biology, and psychology. The field of olfaction has recently entered the medical clinic, a testimony both to the human significance of this sense modality and to the level of sophistication of present knowledge about it.
With more sophisticated research the relationship between subjective odor experience of humans and objective odor-guided behavior of animals has become clearer, and is an indication of the development of scientific understanding. According to the present multi-author review, this development can be summarized under four main headings: the olfactory stimulus, its transduction into a neural response, the neuroscience of the olfactory system, and the plasticity of the perception and behavior elicited by olfactory stimuli.
Finally, Gesteland presents the conclusion, and it is a timely statement about the present state of the science of smell as revealed in present topical reviews augmented by his own broadly based research ranging from biochemistry to psychophysics.

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Ontogeny of the olfactory code

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Key words. Olfaction; olfactory bulb; olfactory epithelium; odor-guided behavior development.

In altricial species, such as the rat, olfactory system development is precocious compared to other sensory systems and its function is necessary for early postnatal survival. Apart from its importance in the control of early behaviors, the developing olfactory system has a number of features that are of more general interest to chemosensory scientists and developmental neurobiologists. In mammals, the synaptic mechanisms of the olfactory bulb undergo considerable postnatal modifications. Understanding the ontogeny of the bulb provides information about the maturation of interneuronal pathways, the biological basis of early learning, as well as the neural substrate that is necessary for, at least, the rudimentary olfactory capabilities exhibited by the newborn pup. The olfactory bulb has afferent connections with a number of structures in the basal forebrain and receives efferents from several of its projection areas as well as from important cholinergic, noradrenergic, and serotonergic systems. With its simplified morphology, the bulb presents a useful model system for studying the factors that control the formation of neuronal connections within the brain and the effects of neurotransmitter systems on these processes.
The maturation of olfactory receptor neurons involves very different processes and follows a very different time course from that of the olfactory bulb. In the rat, a substantial portion of receptor cells exhibit mature properties at birth. As in other vertebrate species, these neurons have an apparent lifespan of 30-60 days and thus are constantly being replaced and undergoing differentiation in animals of all ages. For the physiologist, the turnover of receptor cells raises two fundamental issues. First, how does an organism achieve perceptual constancy with the unending turnover of synaptic inputs driving second order neurons. Second, how do the properties of receptors change as they differentiate and how might these differences bias experiments that attempt to describe the nature of the olfactory code among those (mature) neurons that are synaptically connected to the brain.
This paper will focus broadly on the developmental plasticity of olfactory neurons. In interest of coherence, it will concentrate on experiments related to the rat, a species for which the ontogeny of olfaction has been described in anatomical, physiological, and behavioral studies.

The ontogeny of odor-guided behavior

Suckling is the most conspicuous behavior exhibited by the newborn rat pup. During the first postnatal week pups depend on olfactory cues to locate their mothers' nipples. When suckling is measured on anesthesized dams, alterations in thermal (cooling the mother) or tactile (shaving the mother) cues have small effects on nipple attachment. In contrast washing the nipples to eliminate olfactory cues abolishes suckling in 3–4-day-old pups and reapplication of an extract of the nipple wash or pup saliva re-establishes this behavior[5].