

Olfactory Subsystems in Mammals: Specific Roles in Recognizing Chemical Signals?

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Introduction

Animals survey their external environment for relevant chemicals including compounds which are important for finding food sources and habitats but also for social interaction and reproduction. In mammals, these chemical signals are received by divergent chemosensory subsystems: the main olfactory epithelium which is considered to be responsible for the reception of general odorants, the vomeronasal organ (VNO) which is thought to mediate the detection of substances carrying specific information concerning species, gender and identity of an animal, and a small epithelial patch on the nasal septum at the entrance to the nasopharynx called the septal organ (SO), which by virtue of its exposed position in the respiratory air stream, has been proposed to play an alerting role (Figure 1).

The OR37-system of the olfactory epithelium

The capability to detect and discriminate myriads of odors is based on the distinct chemospecific responsiveness of multiple olfactory neuron populations. The characteristic response spectrum of each population is due to the odorant receptor subtype expressed in the cells. Out of a repertoire of about thousand receptor genes, the olfactory sensory neurons appear to express only one receptor type, which renders the cell's responsiveness selective but rather non-specific. Consequently, each cell population responds to multiple odorants and each odorant activates several cell populations; the basis for combinatorial coding of odors. Thus, the ability to recognize and discriminate a wide range of odorous molecules is based on the multiplicity and diversity of olfactory receptor types. Accordingly, genes encoding olfactory receptors appear to be under positive darwinian selection pressure which acts in favor of diversification and increase of receptor variability (Hughes and Hughes, 1993). Within the main olfactory epithelium, a population of chemosensory neurons, which express exclusively receptors of the so-called OR37-subfamily, is assembled in a small patch at the tip of central turbinates. These OR37-receptors have a characteristically extended third extracellular loop (Kubick *et al.*, 1997). A comparative analysis of genes encoding OR37 olfactory receptor subtypes in human and

mouse but also in rat and opossum revealed that in spite of a pronounced diversity in non-coding sequence regions, indicative for a long-term coexistence of the genes, the coding regions of the OR37 genes showed remarkably high sequence identity within a species and across species borders (Hoppe *et al.*, 2003). This is a unique feature for olfactory receptors and is probably the consequence of functional constraints. It appears that in contrast to ORs in general, the OR37-receptors are under negative selection pressure. Conservation of the coding sequence across species indicates that the receptor type may be tuned to distinct ligands; it is conceivable that such compounds could be crucial for chemical communication of mammals.

The septal organ

The septal organ is a small island of chemosensory neuroepithelium located bilaterally at the ventral base of the nasal septum at the entrance of the nasopharynx; it is separated from the main olfactory epithelium by surrounding respiratory epithelium. In many aspects, the septal organ appears to resemble the main olfactory epithelium, comprising morphologically similar sensory neurons, which appear to show similar odorant responses, mainly mediated by the cAMP-pathway; also, they project their axon to the main olfactory bulb (Ma *et al.*, 2003). Thus, one could speculate that the septal organ, comprised of only a few thousand sensory neurons, may just be a subsidiary of the main olfactory epithelium. Attempts, to unravel the types and the repertoire of receptors expressed in the SO of mice, indicated that sensory neurons of the SO express OR-types which are also expressed in the MOE. From the ~850 class II ORs only a limited number was expressed in SO, most of them only in a few neurons. However, there was an exception, the receptor type mOR244-3 was expressed in a very high proportion of the cells, indicating that the receptor type OR 244-3 appears to be unique and thus may play a special role in the SO (Kaluza *et al.*, 2003). Concerning the processing of chemosensory information received by the SO, it is interesting to note that there was no evidence for any spatial distribution pattern of the SO neurons. The projection pattern of nerve fibers

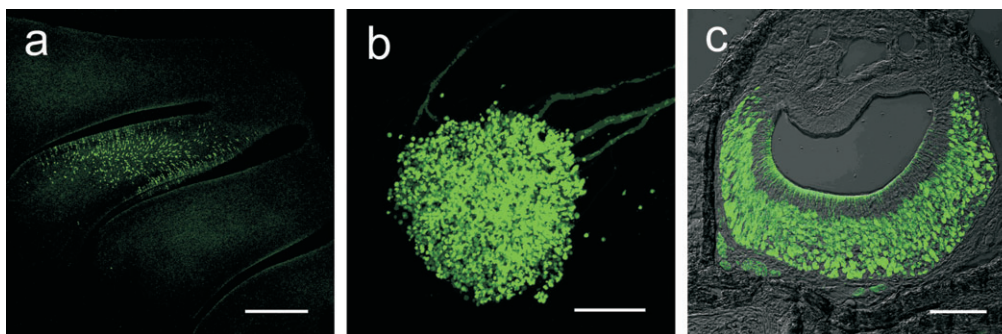


Figure 1 Subsystems of the olfactory system. (a) Cluster of OR37 neurons in the main olfactory epithelium; scale bar = 500 μ m. (b) Septal organ; scale bar = 200 μ m. (c) Vomeronasal organ; scale bar = 200 μ m.

from the SO monitored by DiI-tracing studies using OMP-GFP transgenic mice revealed that SO-axons navigate in highly variable fiber tracts across the MOE; they all pass through the cribriform plate at a spatially distinct site and terminate in the posterior-ventromedial aspect of the bulb. Here, a subpopulation of axons forms a dense mesh on the medial aspect of the bulb, where they terminate in target glomeruli for axons from the MOE, the other subpopulation of axons project to a few 'septal glomeruli', which appear to receive input exclusively from the SO-neurons (Levai and Strotmann, 2003). In spite of the progress, the function of the chemosensory organ remains elusive. In view of the nasal airflow and its exposed location at the entrance of the nasopharynx, it still seems conceivable that the SO may sense odors in the environment even during quiet respiration, when the airstream does not reach the MOE; activation of the SO could subsequently modify the respiratory intensity to increase the airflow over the MOE (Rodolfo-Masera, 1943). The mesh-like co-innervation of multiple glomeruli, which receive the major input from the MOE could be in line with such a general 'monitoring function'. However, it is unclear how this can be accomplished with a very limited and rather specific repertoire of receptor types. The targeting of most SO-fibers in distinct septal glomeruli, suggests the possibility that in addition to an olfactory alerting role, a more specific task may be accomplished by the septal organ.

OR-cell populations in the vomeronasal organ

The vomeronasal organ (VNO) of mammals is a 'specialized nose' which is considered as a detector for pheromones, chemical cues which are emitted by other animals and convey specific information concerning gender and identity; they also induce innate behaviors, such as aggression and mating. Two populations of vomeronasal sensory neurons are distinguished: cells in the apical layer expressing V1R-receptors and G_i -protein, projecting to the anterior part of the accessory bulb and cells in the basal layer expressing V2R receptors and G_o -proteins projection to the posterior part of the accessory bulb (Dulac and Torello, 2003). *In situ* hybridization and analysis of transgenic mouse line have provided evidence, that there is a third population of sensory neurons; these cells express OR-subtypes, which are concomitantly expressed in the main olfactory epithelium. The functional roles of these cells are elusive; however, a recent study indicate that some odorants may be detected by the VNO (Trinh and Storm, 2003). Experiments towards a molecular phenotyping of these cells have indicated that the OR-expressing cells in the VNO do not express adenylyl cyclase Type III or G_{olf} , suggesting that at least some OR-subtypes appear to be promiscuous concerning G-protein coupling. All olfactory neurons in the MOE expressing a distinct OR-receptor type project to a common glomerulus. Analysis of transgenic mice visualizing OR-expressing cells and their axons revealed that the labeled nerve fibers from the VNO did not project to the main olfactory bulb but terminated in the anterior region of the accessory olfactory bulb. This characteristic wiring pattern of OR-expressing cells in the VNO and MOE suggest that certain odorants may act as both odors and pheromones.

Conclusion

Recent studies have indicated that the mammalian olfactory system is not uniformly organized but consists of several subsystems each of which probably serve distinct functions.

MOE and VNO are considered as totally independent, consisting of different cell types (cilia versus microvilli) using different transduction cascades and projecting to different brain regions; however, the findings that certain OR-subtypes are expressed in a small population of VNO neurons and reciprocally that certain VR-receptors are ectopically expressed in the MOE (Rodriguez *et al.*, 2000) indicates that the two olfactory systems are probably not completely separate entities. Moreover, the notion that the septal organ may be a subsidiary of the MOE is only partly supported by the molecular phenotyping. The subpopulation of olfactory sensory neurons in the MOE, expressing receptor genes which are under negative Darwinian selection, is probably responsive to distinct set of ligands. Thus, the emerging picture indicates that the olfactory system comprises a variety of morphological, molecular and functional subsystems.

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