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Review Article

Olfactory receptors and the mechanism of odor perception☆

*Ryszard Farbiszewski, Robert Kranc**

School of Medical Science, Białystok, Poland

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ABSTRACT

Introduction: The olfactory system plays one of the key roles in the lives of humans and animals. It can detect thousands of different odor molecules through a large family of olfactory receptors (ORs), of a diverse protein sequence, which are located in olfactory sensory neurons (OSNs) in the olfactory epithelium in the nose of humans, and in the vomeronasal organ in animals. The OR family is comprised of 172 subfamilies, whose members have related protein sequences and are encoded by a single chromosomal locus. The human receptor gene family includes 339 intact receptor genes and 297 receptor pseudogenes, unevenly distributed among 51 different loci on 21 human chromosomes. Different parts of the genome may be involved in the detection of different types of structural odorants.

Odor detection is mediated by odorant receptors. Signals generated in OSNs in response to odorants are transmitted to the olfactory bulb (OB) of the brain, i.e., the first relay station in the control of the olfactory system in mammals. Then, signals are transmitted to the olfactory brain cortex, which has a cortical structure with distinct layers and numerous glomerular modules, and forms a map of olfactory axon terminals. The axonal projection of OSNs is precisely organized with a few topographically fixed glomeruli.

Aim: The purpose of this paper is to present the recent literature in the field of the undertaken subject.

Material and methods: The review of articles is devoted to olfactory receptors and the mechanism of odor perception.

Discussion: In the first part, this review summarizes the mammalian protein ORs that are encoded by genes, as well as the location and structure of these receptors. Extensive studies reveal that mammals can have up to 1000 different OR genes, which constitute approximately 1% of the genomic complement of genes. The analysis of the entire receptor family has shown that it is comprised of 172 subfamilies, whose members are 60% identical in protein amino acid sequence and can recognize odorants with related structures. The second part of this review presents the opinions of many authors concerning the olfactory perception that initiates in the olfactory epithelium. Odor signals are further transmitted to the OB, i.e., the first relay station of the central olfactory system in the mammalian brain. Then such signals ultimately reach higher cortical areas involved

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*Correspondence to: School of Medical Science, Krakowska 9, 15-875 Białystok, Poland. Tel.: +48 85 7499434; fax: +48 85 7499431.
E-mail addresses: r.kranc@wsmed.pl, robertkranc@op.pl (R. Kranc).

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in the conscious perception of odor. At the review's conclusion some diseases associated with smell disorders are discussed.

Results: The olfactory cortex still remains an unexplored and unexplained area in terms of the processing of odorant information. This subject requires further study.

1. Introduction

The sense of smell is a primal sense of enormous significance for humans and animals. The olfactory system was unexplained until 1985. It was known that odorants were detected through receptors located in the epithelium of the nasal cavity in humans, and through the olfactory sense organ, called the vomeronasal organ, in most animals. In the late 1980s Richard Axel, a geneticist from the Institute of Cancer Research of Columbia University, New York, together with Linda Buck, a biochemist from Harvard Medical School, Boston, Massachusetts, began to consider the following questions: How do mammals begin to recognize the vast diversity of odorant molecules that can vary in size, shape, functional groups, and charge? How does odor perception occur? And how is the chemosensory system presented in the brain? These were some of the basic and most challenging questions concerning the field of olfactory research. The olfactory system posed a fascinating problem for these biologists.[7]

Later, it was discovered that a subtle change in the structure of chemical odors dramatically changes their perceived odor. Olfactory sensory neurons (OSNs) that detect odorants express different receptors, elicit different signals in the brain, and thereby, generate distinct odor perception.

Recent *in vivo* and *in vitro* studies have challenged the existing models of olfactory processing in the vertebrate olfactory bulb (OB) and the insect antennal lobe. Lateral connectivity between olfactory glomeruli was previously thought to form a dense, topographically organized inhibitory surrounding. New evidence suggests that lateral connections may be sparse, nontopographic, and partly excitatory. Other recent studies highlight the role of active sensing (sniffing) in the shaping of odor-evoked neural activity and perception.[37]

2. Aim

The purpose of this paper is to present the recent literature in the field of olfactory receptors and the mechanism of odor perception.

3. Material and methods

A review of articles devoted to olfactory receptors and the mechanism of odor perception was performed. Available medical databases PubMed, Scopus, Embase, and ProQuest were used.

4. Discussion

4.1. *Receptors for odorants and pheromones*

Axel and Buck, pioneers in the research of molecular structure of odor and pheromone sensing in animals, employing the technique of gene cloning and other methods (e.g., PCR-reaction), have isolated genes encoding protein-coupled olfactory receptors (ORs) in the human genome. Then, they have determined the chromosomal location of each OR gene, and analyzed the subfamily structure of the human OR family, the chromosome of genes encoding the members of each family, and the subfamily composition of each chromosomal locus.

This has led to the discovery of three distinct families of ORs, each encoded by a multigene family. One family of 1000 genes encodes ORs in the olfactory epithelium.[6] It comprises approximately 1% of the genomic complement of genes, and this family is the largest unit identified in the genome of any species. The other two OR families are expressed in the vomeronasal organ in mammals. They are called: V_1R family with about 35 members,[9] and the V_2R family with about 150 members.[32] Both receptor families are considered to be candidate receptors for pheromones in most mammals, and recognize different types of chemicals, ligands for these receptors.[5] V_2Rs differ clearly from ORs and V_1Rs in having a very large N-terminal extracellular domain. V_2Rs are related to metabotropic glutamate receptors whose large N-terminal domains bind ligands. Short N-terminal extracellular domains in ORs and V_1Rs bind ligands in a pocket that is formed in the membrane by the combination of the transmembrane domain.[36] A single amino acid in the transmembrane domain has been shown to alter odorant specificity.[20] According to the recent studies of Buck, individual ORs recognize multiple odorants, but V_1Rs and V_2Rs might, instead, be selective for specific pheromones – different types of chemicals, ligands for these receptors.

Studies of Buck have indicated that humans have 636 OR genes, 339 of which are intact and therefore likely to encode functional odorant receptors in the olfactory epithelium of the nasal cavity, and 297 OR pseudogenes. It is assumed that mammals can have up to 1000 different OR genes that encode odorant receptors.[4] This comprises approximately 1% of the genomic complement of genes and this family is the largest unit identified in the genome of any species.

The determination of their genomic locations has demonstrated that OR genes are unevenly distributed among 51 different loci on 21 human chromosomes; 38 chromosomal loci have one or more intact genes and are likely to function in odor perception.

An analysis of the entire OR family has shown that it is comprised of 172 subfamilies, whose members are 60% or