Olfaction and Ligand–Receptor Interaction

Subjects: Others
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Odorant or olfactory receptors (ORs) are located in the human nose, in the olfactory epithelium. The olfactory receptors can recognize many different odor molecules of a diverse protein sequence, and OR genes constitute the most abundant family of G protein-coupled receptors (GPCRs). The human receptor gene family comprises 339 receptor genes and 297 receptor pseudogenes, unequally dispersed in 51 distinct loci on 21 human chromosomes. Humans have a compassionate sense of smell, which is essential for discovering odors necessary for maintaining a healthy life, such as the smell of smoke (detection of fire) and rotten food (to avoid ingestion).

Keywords: Olfactory translation ; chemosensory processing system ; G-protein-coupled receptor ; transduction mechanism ; Ca2+ activated Cl− channels

1. Introduction

The peripheral olfactory system was described in 1891 by Santiago Cajal and continues to elude our understanding. In this context, the publication entitled “The Molecular Logic of Smell” by Richard Axel in 1995[1]was significant. It summarises intensively the research done in the late 80s and early 90s, which aimed to study the molecular processes of olfactory translation in the nose´s olfactory epithelium. The olfaction consists of capturing a significant amount of diverse molecular aromas of the natural world, extracting information through personal perceptions related to beverages, flowers, perfumes, and whatever humans encounter daily [2]. According to the same authors, olfaction “(…) is a chemosensory processing system that can detect potentially infinite numbers of low molecular-mass compounds, called odorants, which combine at different concentrations, to elicit this complex perception (…)”[2]. Thus, the olfactory perception results from ORs' reversible interaction with the odorant molecules (OM) (Figure 1).

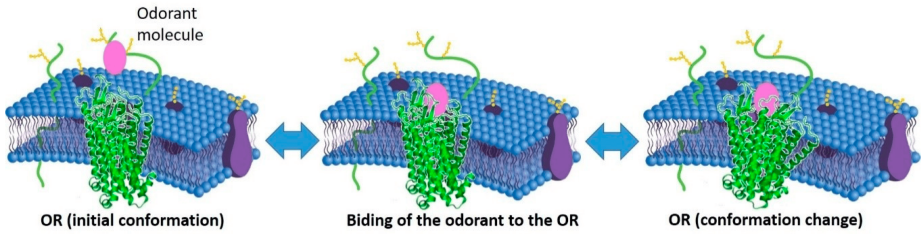

Figure 1. Schematic representation of the interaction between OM (odorant molecule) and the olfactory receptors. This interaction can be analyzed as a sequence of 2 reversible reactions: 1st, the binding of the odorant to the olfactory receptor (OR) and its consequent release, and then, 2nd, the activation (and deactivation) of the OR due to a change of its conformation.

More than one “trillion” (10^{12}) odors can be discriminated[3], and some authors say that “The next generation of rich media services will be immersive and multisensory, with olfaction playing a key role (…) for enhancing user quality of experience”[4].

2. Mechanisms

In mammals, notably in humans, distinct groups of sensory neurons, which integrate several processing routes, constitute the olfactory system. This system comprises both the central olfactory system and the vomeronasal olfactory system. Each neuron in these systems expresses a type of G-protein-coupled receptor (GPCR) superfamily specialized in detecting a specific type of odor. Thus, the environment presents diverse aromas that can be distinguished by the pattern of all sensory neurons that constitute the olfactory system[5]. For instance, humans require seven transmembrane G-protein-coupled receptors to identify natural odorants like pheromones[6].

But how does the transduction mechanism work? According to Villar and co-workers[7], the central olfactory epithelium or olfactory bulb comprises three main cell types: olfactory receptor cells (Figure 2(a)), sustentacular cells, and basal cells. ORCs (olfactory receptor cells) project a single dendrite to the epithelial surface, where it swells, forming the dendritic knob (Figure 2(b)).

Therefore, the initial odor detection process begins in the posterior region of the nose, when volatile molecules enter the nasal cavity (Figure 2), biding, directly or through odorant-binding proteins, to receptors on the external surface of cilia and activate receptors on the olfactory epithelium. After this binding, a complex sequence of biochemical reactions occurs, similar to those found in rod photoreceptors in the human eye, i.e., olfactory receptor neurons contain a G-protein (Golf) protein, in which its Gαolf subunit dissociates from the Gβγ complex (G beta-gamma complex) and activates specific olfactory adenylate cyclase (AC) (Figure 2(c)), generating cyclic adenosine monophosphate (cAMP). Then is observed neuron depolarisation because the increase of the cAMP promotes the opening of the channels and allows cations entry, sodium (Na^+), and mainly calcium (Ca^{2+}) ions. The ensuing increase in intracellular Ca^{2+} opens Ca2+-activated Cl^- channels, causing an extra inner current due to a Cl^- efflux amplifying the olfactory receptor potential depolarization. This depolarisation arises from the cilia until the axon hillock region of the olfactory receptor neuron, where action potentials are generated and transmitted to the olfactory bulb[8]. The axon hillock region of the olfactory receptor neuron, the last receptor of the depolarisation that arises from the cilia, generates and transmits action potentials to the olfactory bulb[9].

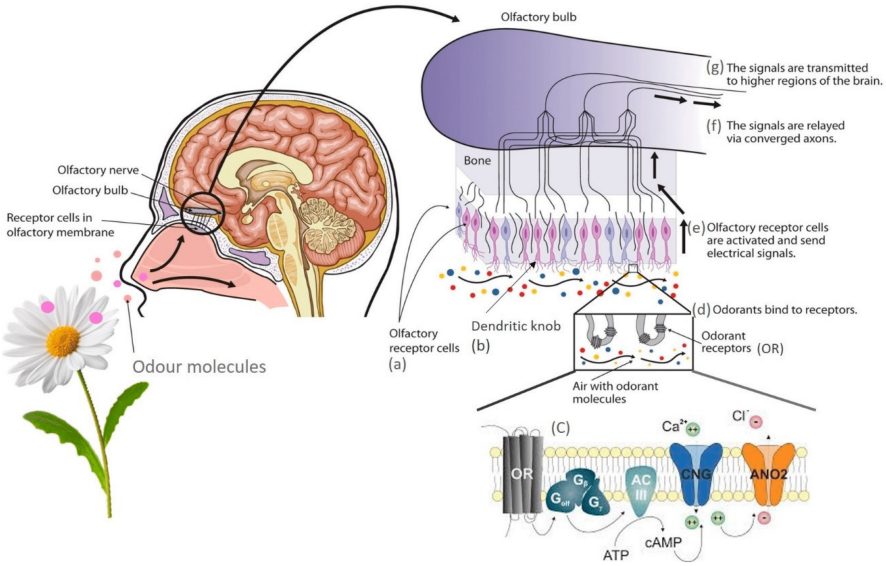

Figure 2. Schematic representation of olfactory transduction mechanism. OR—Odorant receptor protein; Golf—G-protein complex, made up of Gαolf (alpha (α)), Gβ (beta (β)), and Gγ (gamma (γ)) subunits; ACI—Olfactory adenylate cyclase; CNG—Ca^{2+} Cyclic Nucleotide Gated channel; ANO2—Anoctamin Ca^{2+} activated Cl^- channel; ATP—Adenosine triphosphate; cAMP—Cyclic adenosine monophosphate.

Consequently, olfactory transduction can be divided into ligand binding (Figure 2(d)), signal generation, and signal termination (Figure 2(e)), where the age of action potentials is conducted along the axon to the olfactory bulb. The signals are relayed via converged neurons (Figure 2(f)) and then transmitted to higher brain regions (Figure 2(g))[8]. What happens when it is present a mixture of 2 or more odorants? Here, the answer is much more complex. Several authors have done studies in this area, but many questions remain unexplained. According to Bushdid and co-workers[3], since neither the dimensions nor the physical limits of the olfactory stimulus are known, the strategies used for other sensory modalities, namely those used regarding the estimation of the visual and auditory systems' average resolution, are not possible to enforce in the human olfactory system. In the presence of a mixture of two odorants, it is possible to determine the number of receptors activated by any concentration of the mix when, in advance, we know the affinity and efficiency of each of the components of the mixture alone because the OR stimulated with two different odorants will respond with sigmoid curves as concentration's function of the two odorants. Also, the number of ORs activated by the blend can be characterized by a logistic curve when two odorants compete for the same binding site[10][11].

Münch et al.[12]studied how mixtures of odorants interact with ORs supported by olfactory receptor neurons (ORNs) using *Drosophila melanogaster* ORNs. Their results agree with others made in the rat, confirming that the response of an ORN to a binary mixture can sometimes be predicted quantitatively by knowing the ORN responses to its components. Rospars in 2013[13]aiming to answer this question, presented diverse hypotheses of the functioning of the olfactory system based on mathematical models and elementary chemical kinetics. According to the author, on the one hand, whenever the concentration of the odorant molecule increases, the activated ORs follow a hyperbolic curve. On the other hand, the affinity between the odorant and the OR does not depend on the total number of ORs but on the four reversible reactions'

rate (binding vs. release and activation vs. deactivation). Finally, this author also concluded that the maximum number of receptors activated in a given period will depend on the affinity of the OR and the rate constants of the activation-deactivation reaction (but not the release of the binding response)[13].

Nevertheless, some subjectivity is implied in the Humam sensory evaluation of odor. Sometimes, products are not yet ready to be tasted by humans. To circumvent the limitations of the human being, science has arranged a manner of mimicking the human nose. Electronic noses (e-noses) are devices created to recognize volatile odorous compounds. They are designed to mimic the human nose, not in its shape or size, but its ability to entrap odors and sensory transduction mechanisms. E-noses usually possess cross-reactive sensing arrays that, upon odor exposure, generate patterned responses and analytical algorithms that catalog these patterned responses [14][15].

While insects and even sharks depend on their movement through the habitat in which they live to come into contact with sensing elements, mammals can sniff, allowing the connection of the odorants with the receptors, usually inside their nasal cavities. For aroma detection by the e-nose, volatile molecules must come into physical contact with the detectors by moving the carrier air to the sensor or the detector through the air, allowing it to contact the volatiles[14].

E-nose can contain up to 40 sensors, each standardized for a precise chemical compound. Compounds and sensors combined to provide a measurement pattern. The electronic nose can only identify expected and known volatile compound patterns [16]. So, to be able to detect, analyze, and process the information, an e-nose device must be built putting together three components, each with a specific function[17]: A sample delivery system consisting of a multisensory array; a detection system such as an artificial neural network (ANN); and a computing system with appropriated software (digital pattern-recognition algorithms and reference-library databases)[18].

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