Making Sense Of Smell : From Odorant Receptors To The Olfactory Cortex

Swapnil J. Paralikar
Assistant Professor, Department of Physiology, GMERS Medical College, Gotri, Baroda.

Abstract: The olfactory system is uniquely essential for life. Olfactory receptor cells, located in the olfactory mucous membrane.project to the olfactory glomeruli where they synapse with the lateral dendrites of the mitral and tufted cells. This mechanism of lateral inhibition sharpens the olfactory signal enabling differentiation of odours. From the olfactory glomeruli, second –order neurons project to the olfactory cortex which has evolved over millions of years. It consists of an older system (concerned with primitive responses to olfaction) and a newer system (concerned with the conscious analysis of odour). The intriguing question as to how human beings can detect 10,000 different odours was solved by two scientists Drs. Richard Axel and Linda Buck. They unravelled the 1000 different olfactory receptors, each activated by a combination of different odours Genes coding for the olfactory receptors form the largest gene family in humans, larger than the T-cell receptor gene family.

Key Words: Olfaction, olfactory receptors, olfactory cortex

Author for correspondence: Dr.Swapil Parlikar, 18, Taksh Bungalows, Near Shobhana Nagar, Vasna Road, Baroda-390 021. Gujarat, India. E-mail :drsparalikar@gmail.com

Introduction: The olfactory system is uniquely essential for life. Many species rely on their sense of smell to locate food, detect predators or other dangers, navigate and communicate societal information. Olfaction plays a role in mate choice, mother-infant recognition and signaling between members of a group in all species and for marking of territory in big cats. Humans may not rely on olfaction for survival, but we nevertheless use olfaction to gather information on the surrounding e.g. from the mother checking if the milk is still safe for the baby, to the hunter using smell to locate prey, to the wine taster enjoying a vintage Bordeaux. Humans also communicate via odorants and pheromones, both consciously (by applying artificial scents) and subconsciously. For example, olfaction mediates the curious synchronization of menstrual cycles of women living in close proximity. Aesthetically, olfaction is important for enjoyment of our food, our natural environment and our lives in general. In addition, smell rekindles sweet (and sometimes. unpleasant) memories from the past. Smell also has a protective role e.g. the odour of methylmercaptan in natural gas gives a warning signal when only a small amount of gas has leake[1,2].

Recently, a lot of research is focused on the olfactory system to solve the intriguing question : how a simple sense organ and its brain representation that lacks a high degree of complexity can mediate the perception of 10,000 different odours?

Organization Of The Olfactory System: Olfactory mucous membrane: The olfactory receptor cells are located in the olfactory mucous membrane in the roof of the nasal cavity near the nasal septum(Fig 1). In humans, it covers an area of about 5 cm^2; however, in macrosmatic animals like dogs, the area of the olfactory mucous membrane is forty times larger (Fig 2).

The olfactory receptor cells are **bipolar neurons.** each neuron has a short thick expanded dendrite called the olfactory rod; the axons penetrate the cribriform plate of the ethmoid bone and terminate in the olfactory bulb. The dendrites have numerous cilia, on which are located the olfactory receptor cells.

In fact, the olfactory mucosa is the place where the nervous system is closest to the external world.

The olfactory neurons are true neurons, and like the taste receptor cells are continuously being renewed. **Bone morphogenic proteins (BMP)-** growth factors involved in growth in all tissues of the body, are involved in regulating regeneration of the olfactory neurons [3].(Fig. 1 & 2) The phenomenon of **lateral inhibition** sharpens the olfactory signal projecting to the olfactory cortex, and thus enables differentiation of odour[3, 4].(Fig 3).

Each olfactory glomerulus receives input from similar receptor cells. Each receptor projects to two glomeruli (there are about 2000 olfactory glomeruli) Because the olfactory neurons are continuously renewed it is a wonder as to how their axons find their way to the correct glomerulus[3,5,6].

Fig.1. Olfactory mucosa and olfactory receptor cells

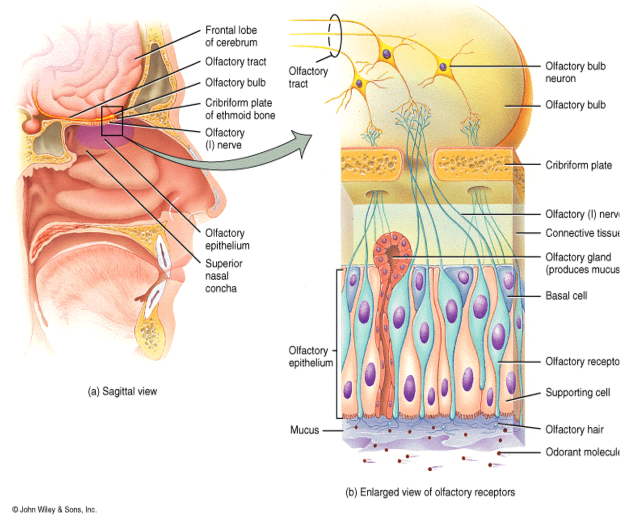
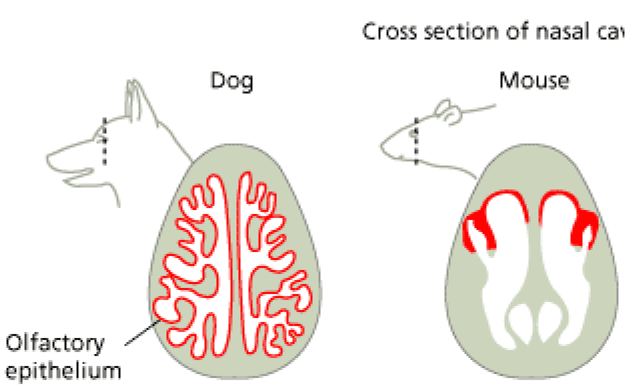
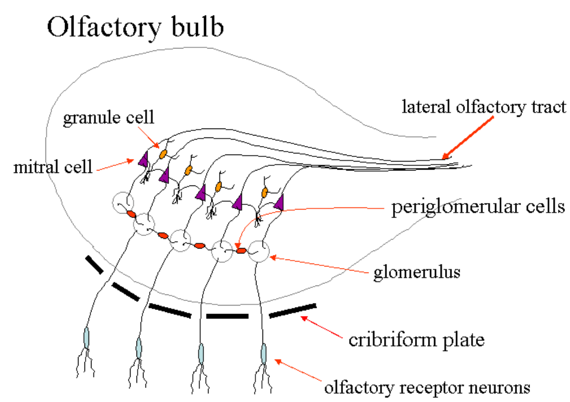


Fig.2. Portion of the nasal cavity occupied by the olfactory mucous membrane in dogs, mice and humans (From www.nobelprize.org)



Olfactory glomeruli: The axons of the olfactory receptor cells terminate in the olfactory bulb, where they synapse in the olfactory glomeruli, with the primary dendrites of the **mitral and tufted cells**. Mitral and tufted cells are second order neurons projecting to the olfactory cortex. In addition, there are **peri-glomerular cells** connecting one glomerulus to the other. Centrifug

Fig. 3. Olfactory glomeruli (From Cardiff.ac.uk)



al fibres project from the olfactory cortex to the olfactory bulb, where **granule cells** synapse with the lateral dendrites of the mitral and tufted cells forming dendro-dendritic synapses. The mitral and tufted cells excite the granule cells by releasing glutamate, while the latter releases GABA inhibiting the mitral and tufted cells. (Fig. 3) .

Olfactory Receptors, Olfactory Genes And The Nobel Prize: The dilemma as to how we can perceive 10,000 different odours was solved by two scientists, **Dr. Richard Axel** and **Dr. Linda Buck** of Columbia University and Harvard University, USA respectively. In a series of pioneering experiments they unravelled the olfactory receptors, genes, cortical representation and related aspects. Subsequently, the 2004 Nobel Prize in Physiology or Medicine was awarded jointly to Axel and Buck [7].(Fig 4).

Fig.4. Drs. Richard Axel and Linda Buck
(Fromwww.nobelprize.org)

Olfactory receptors are **serpentine G –protein coupled receptors with seven transmembrane domains.** Mice have about 1000 different olfactory receptors. Humans have a similar number, although some receptors have been lost in evolution[4]. Unlike other receptors which are specific for a ligand, olfactory receptors bind a number of odorants with different affinities. It is a result of **combinatorial activation** of a number of receptors that a particular odour can be detected [8,9.]

Each olfactory receptor expresses one and only one gene. Thus, the olfactory gene family is the **largest gene family** in humans, larger than the immunoglobulin and T-cell receptor gene family. It comprises about 3 % of the total human genome [3,7.]

Olfactory signal transduction: Binding of the odorant to the olfactory receptor activates the heterotrimeric**G protein (Golf).** Though earlier both IP_3 and cAMP were considered second messengers, current evidence suggests one common pathway for intracellular signaling – **the adenylcylcase-cAMP system**. G protein activation of adenylcyclase results in the production of a cyclic nucleotide, cAMP. This directly opens ion channels, causing an inward directed current carried by Na^+ and Ca^+ ions. Olfactory sensory neurons maintain a high intracellular concentration of Cl^- ions, and increase in intracellular concentration of $Ca^{+\ 2}$ causes the opening of Ca^{+2} activated Cl^- channels, that produce an efflux of Cl^-, contributing to olfactory neuron depolarization. The depolarization is conveyed along the axon of the olfactory receptor cell to the olfactory glomeruli

The described molecular mechanism of olfactory transduction has several important physiological consequences :

Cascade Effect- The amplification of the transduction cascade allows the production of an electrical quantal event even by binding of a single odorant molecule.

Adaptation – At the level of the transduction the physiological processof adaptation occurs. This is mediated by Ca^{+2} acting via calmodulin to desensitize cAMP-gated channels[1, 10, 11, 12, 13]

Olfactory Pathway: The fibres emerging from the olfactory bulb form the olfactory tract (cranial nerve I). These fibres enter the brain at the junction of the cerebrum and mesencephalon, and divide into a medial olfactory striae and a lateral olfactory striae.

Based on evolutionary studies, the olfactory pathway is divided into :The Very Old Olfactory system- the Medial Olfactory PathwayThe Less Old Olfactory System-the Lateral Olfactory Pathway

The Newer Pathway: **The Very Old Olfactory Sytem-The Medial Pathway**

The **medial olfactory striae** consists of fibres from the anterior olfactory nucleus, which consists of multipolar neurons scattered within the olfactory tract. Some of these fibres terminate in the **septal nuclei,** a group of nuclei located anterior to the hypothalamus. Others cross the midline in the anterior commissure and inhibit mitral cell activity in the contralateral bulb (by exciting granule cells there). The result is a relative enhancement of the more active bulb, providing a directional cue to the source of olfactory information.

In addition, the median forebrain bundle links the olfactory system with areas in the hypothalamus and brainstem.Both these pathways are concerned with primitive responses to olfaction, including licking lips, chewing, salivation, etc. This is the most ancient of the olfactory pathways.

Less Old Olfactory System –The Lateral Pathway: The lateral olfactory striae terminates in the **piriform lobe** of the anterior temporal cortex . The human piriform lobe includes the cortical part of the amygdala, the uncus, and the anterior end of the parahippocampalgyrus
This pathway is concerned with smell preferences (liking and disliking a particular odour), and aversion to unpleasant odours.

The Newer Pathway: A part of the olfactory tract terminates in **dorsomedian nucleus of the thalamus,** and from then projects on to the **orbitofrontal cortex** . This is the highest pathway for olfactory discrimination concerned with the conscious analysis of odour [14,15] (Fig. 5 to be inserted here).

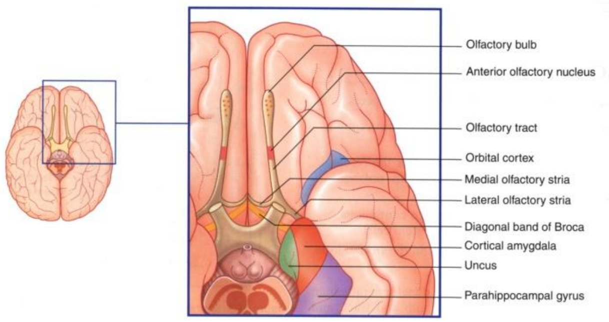


Fig.5. Olfactory pathway and olfactory cortex

Targetting Of Odorant Receptors To The Olfactory Cortex: The olfactory receptors are organized in a topographical manner in the olfactory bulb. However, such topographical representation is lacking in the olfactory cortex. Instead, odorant receptors seem to be mapped to multiple, discrete clusters of neurons in the olfactory cortex. Studies were carried out in transgenic mice using barley lectin as a neuronal tracer. Two olfactory receptors M5 and M20 were studied. It was found that mitral cells carrying input from these receptors form synapses in most olfactory cortical areas and are organized in discrete clusters. Moreover, by comparing the location of neuronal clusters in different animals, it was found that there is a stereotyped map of sensory inputs to the olfactory cortex, where odorant receptors are targeted to **multiple, discrete, but partially overlapping clusters of olfactory neurons**[16].

Abnormalities In Odor Detection: Anosmia (inability to smell) and hyposmia or hypesthesia (diminished olfactory sensitivity) can result from simple nasal congestion or be a sign of more serious problem including damage to the olfactory nerves due to fractures of the cribriform plate, tumors such as neuroblastoma or meningiomas, or infections (such as abscesses). Alzheimer's disease can also damage the olfactory nerves. Aging is also associated with abnormalities in smell sensation; more than 75% of humans over the age of 80 have an impaired ability to identify smells.

Hyperosmia (enhanced olfactory sensitivity) is less common than loss of smell, but pregnant women commonly become oversensitive to smell. Dysosmia(distorted sense of smell) can be caused by several disorders including sinus infections, partial damage to the olfactory nerves, and poor dental hygiene.

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Source Of Financial Support-Nil
Conflict Of Interest-None