

## PHYSIOLOGICAL BASIS OF OLFACTION

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### ABSTRACT

*The olfactory system represents one of the oldest sensory modalities in the phylogenetic history of mammals. As a chemical sensor, the olfactory system detects food and influences social and sexual behavior. Within the nasal cavity, the turbinates or nasal conchae serve to direct the inspired air toward the olfactory epithelium in the upper posterior region. This area contains more than 100 million olfactory receptor cells. An understanding of the anatomical and physiology of Olfactory System has been given in this review.*

**Key words:** *Olfaction, olfactory system*

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### INTRODUCTION

The capability to detect various volatile chemicals is one of the primary function of nose which helps to differentiate between thousands of largely organic, low molecular weight, volatile compounds (1).

### MICROANATOMY

The olfactory system is one of the oldest sensory modalities in the phylogenetic history of mammals.

The olfactory epithelium consists of four distinct cell types.

1. Olfactory cells.
2. Supporting cells
3. Basal cells
4. Brush cells

### Olfactory Cells

These are bipolar neurons which congregate to form the olfactory nerve. The olfactory nerves go through the cribriform plate and terminate on the dendrites of the mitral cells located in the glomeruli of the olfactory bulb. The apical poles of these neurons are covered with non-motile cilia, with the plasma membrane containing odorant-binding proteins acting as olfactory receptors. The incoming odorants are made soluble by the serous secretion from Bowman's glands, located in the lamina propria of the mucosa.

### SUPPORTING CELLS

Also called as the sustentacular cells and function as metabolic and physical support for the olfactory cells. On microscopy these are pseudo stratified ciliated columnar epithelium and their nuclei is more apically located.

### BASAL CELLS

These cells lie on the basal lamina of the olfactory epithelium and are the stem cells which are capable of division and differentiation into either supporting cells or olfactory cells which in turn leads to the olfactory epithelium being replaced every 2 to 3 weeks (2). The Basal cells can be divided on the basis of cellular anatomy histological markers into two populations: the horizontal basal cells which line the olfactory epithelium and the slightly more superficial globose basal cells (3).

Horizontal basal cells are now thought to be the primary stem cell population supplying new cells in this system (4).

### BRUSH CELLS

A microvilli-bearing columnar cell with basal surface in contact with afferent nerve endings, specialised for transduction of general sensation. Nerve fibres are terminal branches of trigeminal nerve

(cranial nerve V), rather than the olfactory nerve.

### **BOWMAN'S (OLFACTORY) GLANDS**

These are tubuloalveolar serous secreting glands lying in the lamina propria of the mucosa. These glands deliver a proteinaceous secretion via ducts onto the surface of the mucosa. The role of the secretions are to trap and dissolve odiferous substances for the bipolar neurons. Constant flow from the Bowman's glands allows old odors to be constantly washed away (2).

#### **The Sense of Smell:**

##### **The reception of molecules**

In the 1<sup>st</sup> Century BC, Epicurean and atomistic Roman philosopher Lucretius speculated, different odors are attributed to different shapes and sizes of "atoms" that stimulate the olfactory organ (5). In the present era the theory was supported by the cloning of olfactory receptor proteins and subsequent pairing of odor molecules to specific receptor proteins. Each odor receptor molecule recognizes only a particular molecular feature or class of odor molecules. Mammals have about a thousand genes that code for odor reception. This theory was postulated by Linda B. Buck and Richard Axel (who were awarded the Nobel Prize in 2004) (6). Each olfactory receptor neuron expresses only one functional odor receptor (7). These odor receptor nerve cells work like a lock and key system i.e. if the volatile molecule of a chemical can fit into the lock then the nerve cell will respond. Humans have far fewer active odor receptor genes than other primates and other mammals (8).

##### **Olfactory Perception**

The perception of odors starts when odors molecules activate olfactory receptors present in the olfactory sensory neurons of the olfactory epithelium. Odour molecules are transported across the mucus that covers the olfactory epithelium. Regulation of the olfactory mucus occurs through adrenergic, cholinergic and peptidergic stimulation which may affect the degree of odor perception. The level of stimulation is

determined by airflow direction, velocity and volume. Normally about 15% of the inhaled air passes to this area which is increased on sniffing due to increase in turbulence.

Olfactory receptors are G-protein coupled receptor (GPCR) superfamily and have a 7 transmembrane domain (6). These seven hydrophobic transmembrane domains differ in their amino acid sequence in the transmembrane domain III, IV, and V which suggests that these parts are responsible for discrimination of odors (9).

#### **Signaling molecules and channels**

##### **1. Cyclic adenosine monophosphate formation.**

The binding of the odorant to the receptor changes the conformation of its plasma membrane receptors. The activated receptors catalyzes the exchange of guanosine 5-diphosphate (GDP) for guanosine 5-triphosphate (GTP) on multiple trimeric G proteins causing the dissociation of G $\alpha$  from G $\beta$  and  $\gamma$  (10). G $\alpha$  in activates adenylyl cyclase type III that converts adenosine triphosphate (ATP) into Cyclic Adenosine Monophosphate (cAMP) (11, 12).

The rise in ciliary cAMP opens a cyclic nucleotide gated cation channel, allowing the influx of Na<sup>+</sup> and Ca<sup>++</sup>, and release of K<sup>+</sup>. This results in depolarization of the cell and the firing of action potentials along the axon to the glomeruli, which are globose structures located in the outer part of the olfactory bulb (13). This provides amplification of odor binding events as the activation of one olfactory receptor activate multiple G- proteins and a subsequent cascade of cAMP production.

##### **2. Cyclic Neucleotide gated channels:**

These channels play a significant role in chemo electrical conversion in olfactory cilia. cAMP binds to the CNG channels in the OSN membrane which opens them and the cell becomes highly permeable to Ca<sup>2+</sup> which causes depolarization. CNG channels also allow Na<sup>+</sup> to flow into the cell. The increased Ca<sup>2+</sup> concentration inside the cell activates Ca<sup>2+</sup>-dependent chloride (Cl<sup>-</sup>) channels, which causes intracellular Cl<sup>-</sup> ions to flow out of the cell augmenting the

depolarization event. This depolarization stimulates an action potential that ultimately signals the reception of the odorant. In addition to cAMP gated ion channels, a small subset of OSNs also has cGMP-selective CNG channels (14).

### 3. Calcium activated chloride channels:

The Ca<sup>2+</sup>-activated Cl<sup>-</sup> current was found to be part of the odorant-induced current in amphibian (15) and mammalian OSN (16). This finding provided an explanation for the observation that the olfactory response persisted even in the absence of external Na<sup>+</sup> (17, 18). Ca-activated Cl channels are present in the ciliary membrane (15, 19). The increase in Ca<sup>2+</sup> concentration inside the cilia activates a Cl<sup>-</sup> current (15, 16, 19, 20)

OSNs maintain an unusually high internal concentration of Cl that is in the same range of the Cl concentration present in the mucus at the external side of the cilia (21, 22, 23, 24). In physiological conditions, the opening of Ca-activated Cl channels in the ciliary membrane causes an efflux of Cl ions from the cilia, corresponding to an inward current that further contributes to the depolarization of OSNs (15, 16, 19, 20)

During olfactory transduction, the secondary Ca-activated Cl current plays the important role of a high-gain and low-noise amplifier of the primary CNG current (25, 26, 27, 28), this contributes between 50% and 85% of the total odorant-induced current (16, 20, 24).

### 4. Calmodulin and its effect on Calcium activated chloride channels.

Calmodulin (CaM) (an abbreviation for CALcium-MODULated proteIN) is a calcium-binding messenger protein. CaM is a multifunctional intermediate messenger protein that transduces calcium signals by binding calcium ions and then modifying its interactions with various target proteins (29, 30).

Triggered by Ca influx during odor detection, CaM reduces ciliary cAMP through activation of phosphodiesterase (31), and by inhibition of adenylyl cyclase (AC III), which is a substrate for the CaM-

dependent protein kinase CaMK II (32). Moreover, CaM desensitizes the cAMP-gated channel to its ligand and thereby promotes channel closure and rapid adaptation.(33) The inhibitory effects of Ca-CaM restrict the activity of the cAMP-gated channels to a short time period. The transient Ca influx during this period causes a prolonged elevation of the ciliary Ca concentration and, hence, the opening of multiple Cl channels, as there are eightfold more Cl channels in the ciliary membrane than cation channels. Consequently, the initial small Ca influx triggers a much larger Cl efflux and generates an excitatory receptor current with Cl as the main charge carrier and this causes anion based signal amplification. Hence calmodulin controls both the excitatory and inhibitory processes and serves as a link between the two types of transduction channels (34).

### Olfactory Transduction and adaptation.

The Olfactory (OLFR) gene family is one of the largest in the mammalian genome, comprising about 900 genes in human (~3% of the total genome). Buck and Axel has converged on a set of transduction mechanisms, involving G-protein-coupled second-messenger systems, and neural processing mechanisms, involving modules called glomeruli, that appear to be adapted for the requirements of different species.

The G-Proteins initiate a cascade of intracellular signaling events leading to the generation of an action potential that is propagated along the olfactory sensory axon to the brain (35). The initial signaling is mediated by three distinct families of OLFR, each encoded by a multigene family. The OLFRs are extremely diverse in amino acid sequence, consistent with an ability to recognize a wide variety of structurally diverse odorants. In the olfactory epithelium, OLFRs couple to the GN-AlphaS, the GTP-bound form of G-Alpha-Olf (Olfactory G-protein), which stimulates ACIII (Type III Adenylyl Cyclase) and an increase in cAMP (cyclic Adenosine-3', 5'-Monophosphate) that opens CNG (Olfactory Cyclic Nucleotide-gated) Channels causing membrane depolarization (36). CNGs open to allow an influx of Na<sup>+</sup> and Ca<sup>2+</sup> into the cilia, leading to the generation of an action potential, which transduces signals to the olfactory

bulb. The ligand sensitivity and selectivity is accomplished by the assembly of three different channel subunits, Alpha3, Alpha4, and Beta1b. Later, Ca<sup>2+</sup> is pumped out of ORNs by Na<sup>+</sup>/Ca<sup>2+</sup> exchangers, Cl<sub>Cn</sub> Channel and Ca<sup>2+</sup>-ATPases present in the cilia and dendritic knobs, thus maintaining Ca<sup>2+</sup> homeostasis and returning the cell to electrical neutrality. Other modulators, such as calcium-binding protein Calm (Calmodulin) regulate changes in intracellular Ca<sup>2+</sup> concentrations. The CNG channel protein harbors a binding site for the Ca<sup>2+</sup>/Calm complex. As soon as Ca<sup>2+</sup>/Calm bind to the CNG channels, the channels reduce their sensitivity to cAMP, and close again. Moreover, Ca<sup>2+</sup>/Calm activate an enzyme called PDE (Phosphodiesterase) that transforms cAMP to 5'AMP. Thus, although the odorant is still present, the excitation of the cell is strongly reduced.

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Other second messengers, such as cGMP (cyclic Guanosine Monophosphate), are also produced by odorant stimulation. The decrease in cGMP concentration leads to closure of CNG channels, resulting in two effects, a decrease in Ca<sup>2+</sup> influx and hyperpolarization of the membrane potential. The resulting decrease in intracellular Ca<sup>2+</sup> concentration is important for adaptation. Lowered intracellular Ca<sup>2+</sup> concentration disinhibits GCAP (Guanylate-Cyclase-Activating Protein), leading to activation of GC (Guanylate Cyclase) and resynthesis of cGMP. A second cGMP-regulated element that has been discovered in olfactory neurons is the cGMP-activated PDE2. PDE2 is expressed with GC in a subset of olfactory

neurons. RGS (Regulators of G-protein Signaling) suppress GPCR (G-Protein Coupled Receptors) mediated signals by accelerating the hydrolysis of GTP bound to the G-Alpha subunit (37, 38).

### CENTRAL OLFACTORY PROCESSING

Axons from the olfactory sensory neurons converge in the olfactory bulb to form tangles called glomeruli (singular glomerulus). Inside the glomerulus, the axons contact the dendrites of mitral cells and several other types of cells. Mitral cells send their axons to a number of brain areas, including the anterior olfactory nucleus, piriform cortex, the medial amygdala, the entorhinal cortex, and the olfactory tubercle (39).

The piriform cortex is probably the area most closely associated with identifying the odor

### OLFACTORY BULBS

In humans, the olfactory bulb is located anteriorly with respect to the cerebral hemisphere and remain connected to it only by a long olfactory stalk. After passing the cribriform plate the olfactory nerve fibers branch olfactory nerve layer. When these axons reach the olfactory bulb the layer gets thicker and they terminate in the primary dendrites of the mitral cells and tufted cells. Both these cells send axons to the olfactory cortex and appear to have the same functionality. The axons from several thousand receptor neurons converge on one or two glomeruli in a corresponding zone of the olfactory bulb; this suggests that the glomeruli are the unit structures for the olfactory discrimination. Olfactory bulb contains two types of cells with inhibitory properties: per glomerular cells and granule cells. The per glomerular cells will connect two different glomeruli, and the granule cells, without using any axons, build a reciprocal synapse with the lateral dendrites of the mitral and tufted cells. By releasing GABA the granule cell on the one side of these synapse are able to inhibit the mitral (or tufted) cells, while on the other side of the synapses the mitral (or tufted) cells are able to excite the granule cells by releasing glutamate.

Nowadays about 8,000 glomeruli and 40,000 mitral cells have been counted in young adults. Unfortunately this huge number of cells decrease progressively with the age compromising the structural integrity of the different layers.

## OLFACTORY CORTEX

The axons of the mitral and tufted cells pass through the granule layer, the intermediate olfactory stria and the lateral olfactory stria to the olfactory cortex. This tract forms the bulk of the olfactory peduncle. The primary olfactory cortical areas can be easily described by a simple structure composed of three layers: a broad plexiform layer (first layer); a compact pyramidal cell somata layer (second layer) and a deeper layer composed by both pyramidal and no pyramidal cells (third layer) Furthermore, in contrast to the olfactory bulb, only a little spatial encoding can be observed; "that is, small areas of the olfactory bulb virtually project the entire olfactory cortex, and small areas of the cortex receive fibers from virtually the entire olfactory bulb" (40). In general the olfactory tract can be divided in five major regions of the cerebrum: The anterior olfactory nucleus, the olfactory tubercle, the piriform cortex, the anterior cortical nucleus of the

amygdala and the entorhinal cortex. Olfactory information is transmitted from primary olfactory cortex to several other parts of the forebrain, including orbital cortex, amygdala, hippocampus, central striatum, hypothalamus and mediodorsal thalamus.

In humans, the piriform cortex can be activated by sniffing, whereas to activate the lateral and the anterior orbitofrontal gyri of the frontal lobe only the smell is required. This is possible because in general the orbitofrontal activation is greater on the right side than on the left side, this directly implies an asymmetry in the cortical representation of olfaction.

## SUMMARY

In the last few decades there has been a tremendous amount of advancement in understanding the physiology of Olfaction but still there are some unturned stones which might help in better understanding of Olfactory adaptation, integration of Olfactory subsystems and above understanding the association of Olfaction and Taste. Recent advances in the field of imaging, stem cell research and molecular biology have brought us a step closure but still many arenas are to be explore.

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