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Review Article

Recent concepts about sense of smell, odorant receptors and physiology of olfaction- an insight

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Abstract

The sense of olfaction reached its zenith in development much earlier than other special senses. Olfaction is much more acute than the other senses, exhibits both high sensitivity for odours and high discrimination between them. This plays a very important role even in the social and behavioral aspects of human beings. Recent studies using molecular genetics, electrophysiology and behavioral analysis have elucidated the mechanism, connectivity and functions of olfaction in different organisms. This review is a general topic of interest and discusses the recent advancements regarding the chemical nature of human olfactory receptors, mechanism of olfactory transduction, nomenclature and families of olfactory receptors, olfactory coding, smell discrimination in different animals and olfactory memory.

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Introduction

Olfaction, also known as olfactics, is the sense of smell. This sense is mediated by specialized sensory cells of the nasal cavity of vertebrates, which can be considered as analogous to sensory cells of the antennae of invertebrates. Olfactory receptors are also called as odorant or smell receptors, which are the proteins capable of binding the odor molecules that play a central role in the sense of smell. In humans, olfaction occurs when odorant molecules bind to specific sites on the olfactory receptors (March et al., 2015). These receptors, detecting the presence of smell, are the first order neurons. The axons of these cells join to form the olfactory nerves. They penetrate the cribriform plate of the ethmoid and end in the olfactory bulb or lobe (a brain structure, directly above the nasal cavity and below the frontal lobe) (Schacter et al., 2011), by making synaptic connections with the dendrites of large mitral cells and smaller tufted cells. These mitral cells and tufted cells form conspicuous spherical structures called olfactory glomeruli. The axons from these cells are the second order neurons which form the olfactory tract ending in the olfactory cortex. Olfactory cortex comprises anterior olfactory nucleus, pre-piriform area and piriform cortex, pre-amygdaloid cortex, amygdaloid nucleus, and entorhinal cortex (Fig). Many vertebrates, including most mammals and reptiles, have two distinct olfactory systems including the main olfactory system, and the accessory olfactory system (used mainly to detect pheromones). In air-breathing animals, the main olfactory system detects volatile chemicals and the accessory olfactory system detects fluid-phase

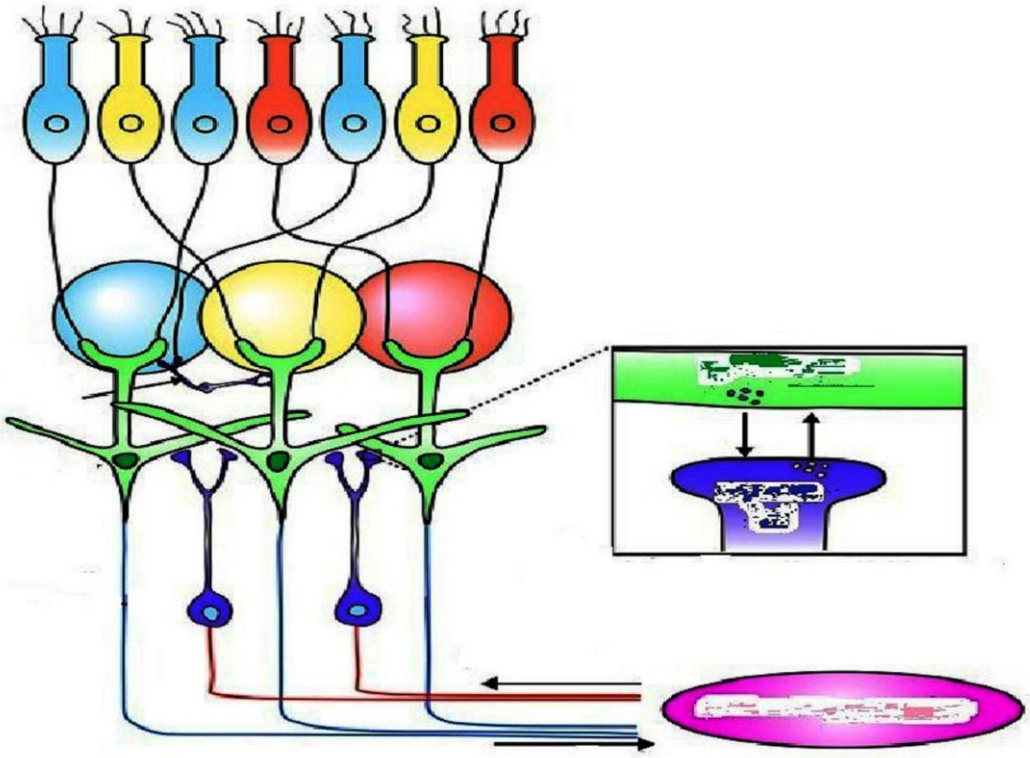

Fig. Neural circuit of olfaction in mammals

[Olfactory sensory neurons (OSNs) expressing the same odorant receptors (blue, yellow, red) project and converge their axons into the same glomeruli. ONSs form excitatory synapses with mitral cells. Mitral cells project their axons to the olfactory cortex. Mitral cells form dendrodendritic synapses with granule cells. Granule cells receive centrifugal glutamatergic inputs from the olfactory cortex].

chemicals (Hussain et al., 2009). Olfaction, along with taste, is a form of chemoreception. The chemicals, which activate the olfactory system in general, at very low concentrations, are called odorants. Although taste and smell are separate sensory systems in land animals, water-dwelling organisms often have one chemical sense (Boroditsky, 1999). Volatile small molecule odorants, non-volatile proteins, and non-volatile hydrocarbons may all produce olfactory sensations. Some animal species are able to smell carbon dioxide in minute concentration (Keller and Vosshall, 2008).

A widely publicized study suggested that humans can detect more than one trillion different odors (Bushdid et al., 2014). This finding has however been disputed. Critics argued that the methodology used for the estimation was fundamentally flawed, showing that applying the same argument for better-understood sensory modalities such as vision or audition, leads to wrong conclusions.

This review is a general topic of interest and discusses the recent advancements regarding the chemical nature of human olfactory receptors, mechanism of olfactory transduction, nomenclature and families of olfactory receptors, olfactory coding, smell discrimination in different animals, and olfactory memory.

History and discovery

The sense of smell has been a topic of debate from humankind's earliest days. The Greek philosopher Democritus of Abdera (460-360 B.C.) speculated that we smell "atoms" of different size and shape that come from objects (Allen, 1991). His countryman Aristotle (384-322 B.C.) on the other hand, guessed that odors are detected when the "cold" sense of smell meets "hot" smoke or steam from the object being smelled (Johansen, 1996). It was not until the late eighteenth century that most scientists and philosophers reached agreement that Democritus was basically right: the smell of an object is due to volatile or easily evaporated molecules, which emanate from it.

In 1821, the French anatomist, Hippolyte Cloquet, rightly noted the importance of smell for animal

survival and reproduction (Friedrich et al., 2012). But his theory about the role of smell in human sex as well as mental disorders, proved controversial. Many theories of the nineteenth century seem irrational or even malignant today. Many European scientists of that period fell into the trap of an essentially circular argument, which held that non-Europeans were more primitive and therefore had a more developed sense of smell. The first half of the twentieth century saw real progress in making the study of smell more rational. The great Spanish neuroanatomist Santiago Ramón y Cajal (1852-1934) traced the architecture of the nerves leading from the nose to and through the brain (Figueres-Oñate et al., 2014). Other scientists carried out the first methodical investigations of how the nose detects scent molecules, the sensitivity of the human nose and the differences between human and animal olfaction. But much real progress on the workings of this remarkable sense has had to wait upon the recent application of molecular science to the odor-sensitive cells of the nasal cavity.

Evolution

There are a large number of different odor receptors, with as many as 1,000 in the mammalian genome which represents approximately 3% of the genes in the genome. However, not all of these potential odor receptor genes are expressed and functional. According to an analysis of data derived from the human genome project, humans have approximately 400 functional genes coding for olfactory receptors and the remaining 600 candidates are pseudo genes (Block et al., 2015a).

The olfactory receptor (OR) gene family in vertebrates has been shown to evolve through genomic events such as gene duplication or gene conversion (Nei and Rooney, 2005). Evidence of a role for tandem duplication is provided by the fact that many olfactory receptor genes belonging to the same phylogenetic clade are located in the same gene cluster (Niimura and Nei, 2006). To this point, the organization of OR genomic clusters is well conserved between humans and mice even though the functional OR count is vastly different between these two species (Niimura and Nei, 2005). Such birth-and-death evolution has brought together segments from several OR genes to generate and degenerate odorant binding site configurations, creating new functional OR genes as well as pseudo genes (Nozawa and Nei, 2008).

Compared to many other mammals, primates have a relatively smaller number of functional OR genes. For instance, since divergence from their MRCA (most recent common ancestor), mice have gained a total of 623 new OR genes and lost 285 genes, whereas humans have gained only 83 genes but lost 428 genes (Niimura and Nei, 2007). Mice have a total of 1035 OR genes, but humans have only 387 OR genes (Niimura and Nei, 2007). The 'vision priority hypothesis' states that the evolution of color vision in primates might have decreased primate reliance on olfaction, which explains the relaxation of selective pressure that accounts for the accumulation of olfactory receptor pseudo genes in primates (Gilad et al., 2004). This hypothesis assumed that functional OR genes can be correlated to the olfactory capability of a given animal (Gilad et al., 2004). In this view, a decrease in the fraction of functional OR genes would cause a reduction in the sense of smell; species with higher pseudo gene count would also have a decreased olfactory ability. However, recent evidence has rendered the 'vision priority hypothesis' obsolete because it was based on misleading data and assumptions. This assumption is flawed. Dogs, which are reputed to have good sense of smell (Craven et al., 2010), do not have the largest number of functional OR genes. Additionally, pseudo genes may be functional; 67% of human OR pseudo genes are expressed in the main olfactory epithelium, where they possibly have regulatory roles in gene expression (Zhang et al., 2007). More importantly, the vision priority hypothesis' assumed a drastic loss of functional OR genes at the branch of the OWMs, but this conclusion was biased by low-resolution data from only 100 OR genes (Matsui et al., 2010). High-resolution studies instead agree that primates have lost OR genes in every branch from the MRCA to humans, indicating that the degeneration of OR gene repertoires in primates cannot simply be explained by the changing capabilities in vision (Niimura, 2012).

It has been shown that negative selection is still relaxed in modern human olfactory receptors, suggesting that no plateau of minimal function has yet been reached in modern humans, and therefore, the olfactory capability might still be decreasing. This is considered to provide a first clue to the future human genetic evolution (Pierron et al., 2013).

There are about 1,000 genes in the olfactory gene family (Subrahmanyam, 2007), the largest known family of genes. Each gene produces a different odour receptor protein, which contributes to the ability of animals to smell many different compounds. Animals not only can smell many compounds, but can also distinguish between them. This requires the mechanism that the different compounds stimulate different receptor cells. Consistent with this, evidences indicate that only one olfactory gene is active in any one olfactory receptor cell (Subrahmanyam, 2007). As a consequence, each receptor cell possesses only one type of receptor protein, though it has got many thousands of the particular type on the membrane of the exposed cilia of the cell. Since each cell expresses only one type of receptor protein, there must be large numbers of cells expressing each type of receptor protein to increase the likelihood that a particular odour molecule will reach a cell with the appropriate receptor protein. Once the molecule reaches the matching receptor, the cells can respond (Subrahmanyam, 2007).

Nomenclature and families

A nomenclature system has been devised for the olfactory receptor family (Glusman et al., 2000) and it is the basis for the official Human Genome Project (HGP) symbols for the genes that encode these receptors. The names of individual olfactory receptor family members are in the format “ORnXm", where:

- OR- is the root name (Olfactory Receptor super family).
- n- is an integer representing a family (e.g., 1-56), whose members have greater than 40% sequence identity.
- X -is a single letter (A, B, C ...), denoting a subfamily (>60% sequence identity).
- M- is an integer representing an individual family member (isoform).

For example, OR1A1 is the first isoform of subfamily A of olfactory receptor family 1.

Members belonging to the same subfamily of olfactory receptors (>60% sequence identity) are likely to recognize, structurally similar odorant molecules (Malnic et al., 2004).

Two major classes of olfactory receptors have been identified in humans (Glusman et al., 2001). They are-

- Class I (fish-like receptors) OR families 51-56.
- Class II (tetrapod specific receptors) OR families 1-13.

Expression

In vertebrates, the olfactory receptors are located in both the cilia and synapses of the olfactory sensory neurons (Rinaldi, 2007) and in the epithelium of the human airway (Gu et al., 2014). In insects, olfactory receptors are located on the antennae and other chemosensory organs (Hallem et al., 2006). Sperm cells also express odor receptors, which are thought to be involved in chemotaxis to find the egg cell (Spehr et al., 2006).

Chemical nature

The olfactory receptors belong to seven trans membrane receptors (the chain of amino acids forming the receptor loops seven times through the thickness of the cell membrane). Within the cell membrane, olfactory receptor proteins are oriented in such a way that one end projects outside the cell and the other end projects inside the cell (Subrahmanyam, 2007). The olfactory receptors, like taste receptors are special chemoreceptors, but unlike taste receptors, the receptors of smell are distant receptors (telereceptors). They respond to even vapors of volatile substances. Once stimulated, depolarizing potentials are set up by the opening of Na channels by the activation of G proteins- adenylyl cyclase- cAMP pathway (Subrahmanyam, 2007).

Odorant receptors and olfactory coding

Olfactory receptor molecules are homologous to a large family of other G-protein-linked receptors that includes β-adrenergic receptors and the photopigment rhodopsin (Purves et al., 2001). Odorant receptor proteins have seven membrane-spanning hydrophobic domains, potential odorant binding sites in the extracellular domain of the protein and the ability to interact with G-proteins at the carboxyl terminal region of their cytoplasmic domain. The amino acid sequences for these molecules also show substantial variability, particularly in regions that code for the membrane-spanning domains (Purves et al., 2001).

The specificity of olfactory signal transduction is presumably the result of this variety of odorant receptor molecules presented in the nasal epithelium (Purves et al., 2001). In rodents (the mouse has been the animal of choice for such studies because of its well-established genetics), genes identified from an olfactory epithelium cDNA library have defined about 1000 different odorant receptors, making this the largest known gene family. In humans, the number of olfactory receptor genes is smaller (about 500–750). Since approximately 75% of these genes do not encode full-length proteins, the number of functional human receptors is about 100–200 (Purves et al., 2001). This relatively small number of odorant receptor types may reflect our poor sense of smell compared to the other species. Nevertheless, the combined activity of this number of receptors is easily large enough to account for the number of distinct odors that can be discriminated by the human olfactory system (estimated to be about 10,000). Messenger RNAs for different olfactory receptor genes are expressed in subsets of olfactory neurons that occur in bilaterally symmetric patches of olfactory epithelium defined by the expression of receptors. Genetic analysis shows that each olfactory receptor neuron expresses only one or at most a few of the 1000 or so odorant receptor genes. Thus, different odors activate molecularly and spatially distinct olfactory receptor neurons. In short, individual odorants can activate multiple receptors, and individual receptors can be activated by multiple odorants (Purves et al., 2001).

Mechanism of olfactory receptor action

Olfactory receptors, expressed in the cell membranes of olfactory receptor neurons are responsible for the detection of odor molecules. Activated olfactory receptors are the initial player in a signal transduction cascade which ultimately produces a nerve impulse which is transmitted to the brain. These receptors are members of the class Arhodopsin-like family of G protein-coupled receptors (GPCRs) (Gaillard et al., 2004). The olfactory receptors form a multi-gene family consisting of over 900 genes in humans and 1500 genes in mice (Niimura and Nei, 2003). Rather than binding to specific ligands, olfactory receptors display affinity for a range of odor molecules and conversely a single odorant molecule may bind to a number of olfactory receptors with varying affinities (Buck, 2004), which depend on physio-chemical properties of molecules like their molecular volumes (Saberi and Seyed-allaei, 2015). An odorant will dissolve into the mucus of the olfactory epithelium and then bind to an OR. OR can bind to a variety of odor molecules with varying affinities. The difference in affinities causes differences in activation patterns resulting in unique odorant profiles. Once the odorant has bound to the odor receptor, the receptor undergoes structural changes and it binds and activates the olfactory-type G protein on the inside of the olfactory receptor neuron. The G protein (Golf and/or G_s) (Jones and Reed, 1989) in turn, activates the lyase – adenylate cyclase, which converts ATP into cyclic AMP (cAMP). The cAMP opens cyclic nucleotide-gated ion channels which results in an influx of sodium and calcium ions into the cell, and an efflux of chloride ions depolarizing the olfactory receptor neuron and beginning an action potential which carries the information to the brain.

There are no known structures of any OR. Their sequences exhibit typical class A GPCR motifs, useful for building their structures with molecular modeling (de March et al., 2015a). Golebiowski, Ma and Matsunami showed that the mechanism of ligand recognition, although similar to other non-olfactory class A GPCRs, involves residues, specific to olfactory receptors, notably in the sixth helix (de March et al., 2015b). There is a highly conserved sequence in roughly three quarters of all ORs that is a tripodal metal ion binding site (Wang et al., 2003). Suslick has proposed that the ORs are in fact metalloproteins (mostly likely with zinc, copper and possibly manganese ions) that serve as a Lewis acid site for binding of many odorant molecules. Crabtree, in 1978, had previously suggested that Cu (I) is "the most likely candidate for a metallo-receptor site in olfaction" for strong-smelling volatiles which are also good metal-coordinating ligands, such as thiols (Crabtree, 1978). Zhuang, Matsunami and Block, in 2012, confirmed the Crabtree/Suslick proposal for the specific case of a mouse OR (MOR244-3) showing that copper is essential for detection of certain thiols and the other sulfur-containing compounds. Thus, by using a chemical that binds to copper in the mouse nose, so that copper wasn't available to the receptors, the authors showed that the mice couldn't

detect the thiols. However, these authors also found that MOR244-3 lacks the specific metal ion binding site suggested by Suslick, instead showing a different motif in the EC2 domain (Duan et al., 2012).

In a recent but highly controversial interpretation, it has also been speculated that olfactory receptors might really sense various vibrational energy levels of a molecule rather than structural motifs via quantum coherence mechanisms (Brookes et al., 2007). It has been shown that flies can differentiate between two odor molecules which only differ in hydrogen isotope (which will drastically change vibrational energy levels of the molecule) (Franco et al., 2011). Not only the flies could distinguish between the deuterated and non-deuterated forms of an odorant, but also could generalize the property of "deuteratedness" to other novel molecules. In addition, they generalized the learned avoidance behavior to molecules which were not deuterated but did share a significant vibration stretch with the deuterated molecules, a fact which the differential physics of deuteration (below) has difficulty in accounting for.

It should be noted however, that deuteration changes the heats of adsorption and the boiling and freezing points of molecules (boiling points: 100.0 °C for H_2O vs. 101.42 °C for D_2O; melting points: 0.0 °C for H_2O, 3.82 °C for D_2O), pKa (i.e., dissociation constant: $9.71x10^{-15}$ for H_20 vs. $1.95x10^{-15}$ for D_2O, cf. heavy water) and the strength of hydrogen bonding. Such isotope effects are exceedingly common, and so it is well known that deuterium substitution will indeed change the binding constants of molecules to protein receptors (Schramm, 2007).

It has been claimed that human olfactory receptors are capable of distinguishing between deuterated and undeuterated isotopomers of cyclopentadecanone by vibrational energy level sensing (Gane et al., 2013). However, this claim has been challenged by another report that the human musk-recognizing receptor, OR5AN1 that robustly responds to cyclopentadecanone and muscone, fails to distinguish isotopomers of these compounds in vitro. Furthermore, the mouse (methylmercaptan) methanethiol-recognizing receptor, MOR244-3, as well as other selected human and mouse olfactory receptors responded similarly to normal, deuterated, and carbon-13 isotopomers of their respective ligands, paralleling results found with the musk receptor OR5AN1 (Block et al., 2015b). Therefore, it was concluded that the proposed vibration theory does not apply to the human musk receptor OR5AN1, mouse thiol receptor MOR244-3, or other olfactory receptors examined. In addition, the proposed electron transfer mechanism of the vibrational frequencies of odorants could be easily suppressed by quantum effects of nonodorant molecular vibrational modes. Hence, multiple lines of evidence argue against the vibration theory of smell (Vosshall, 2015). This later study was criticized since it used "cells in a dish rather than within whole organisms" and that "expressing an olfactory receptor in human embryonic kidney cells doesn't adequately reconstitute the complex nature of olfaction..." In response, the authors of the second study state "Embryonic kidney cells are not identical to the cells in the nose... But if you are looking at receptors, it's the best system in the world (Everts, 2015)."

In 2004, Linda B. Buck and Richard Axel won the Nobel Prize in Physiology or Medicine for their work (Buck and Axel, 1991) on olfactory receptors (Buck and Axel, 1991; Press release in 2004). In 2006, it was shown that another class of odorant receptors exists for volatile amines (Liberles and Buck, 2006). This class of receptors consists of the trace amine-associated receptors (TAAR), including the primary biomolecular target of amphetamine and its endogenous analogues, TAAR 1,3- Iodothyronine, a thyroid hormone, is also known to activate the receptor (Miller, 2011).

As with many other GPCRs, there is still a lack of experimental structures at atomic level for olfactory receptors and structural information is based on homology modeling methods (Broadley, 2010).

Diversity of olfactory receptors

The reason for the large number of different odor receptors is to provide a system for discriminating between as many different odors as possible. Even so, each odor receptor does not detect a single odor. Rather each individual odor receptor is broadly tuned to be activated by a number of similar odorant structures (Gilad and Lancet, 2003). Analogous to the immune system, the diversity that exists within the olfactory receptor family allows molecules that have never been encountered before to be characterized. However, unlike the immune system, which generates diversity through in-situ

recombination, every single olfactory receptor is translated from a specific gene; hence, the large portion of the genome devoted to encoding olfactory receptor genes. Furthermore, most odors activate more than one type of odor receptor (Gilad and Lancet, 2003). Since the number of combinations and permutations of olfactory receptors is almost limitless, the olfactory receptor system is capable of detecting and distinguishing between a practically infinite numbers of odorant molecules.

Deorphanization of odor receptors can be completed using electrophysiological and imaging techniques to analyze the response profiles of single sensory neurons to odor repertoires (Smith et al., 2013). Such data open the way to the deciphering of the combinatorial code of the perception of smells (March et al., 2015).

Comparison of smell discrimination in different organisms

There is no doubt that many animals have a sense of smell far superior than humans (Shepherd, 2004). This is why even today, humans use dogs to find lost persons, hidden drugs, and explosives, although research on "artificial noses" that can detect scent even more reliably than dogs, continues. Humans are called microsmatic, rather than macrosmatic, because of their humble abilities of olfaction (Shepherd, 2004). Still, the human nose is capable of detecting over 10,000 different odors (Wright and Smith, 2004); some in the range of parts per trillion of air. Many researchers are beginning to wonder whether smell does not play a greater role in human behavior and biology than has been thought. Illustration by Hans & Cassidy has shown that human mothers can smell the difference between a vest worn by their baby and one worn by other baby only, days after the child's birth. Yet, some olfactory abilities of animals are probably beyond humans. Most vertebrates have many more olfactory nerve cells in a proportionately larger olfactory epithelium than humans, which probably gives them much more sensitivity to odours. The olfactory bulb in these animals takes up a much larger proportion of the brain than humans, giving them more ability to process and analyze olfactory information. In addition, most land vertebrates have a specialized scent organ in the roof of their mouth called vomeronasal organ (also known as Jacobson's organ or the accessory olfactory organ). This organ, believed to be vestigial in humans, is a pit lined by a layer of cells with a similar structure to the olfactory epithelium, which feeds into its own processing part of the brain, called the accessory olfactory bulb (an area of the brain, absent in humans). The vomeronasal sense appears to be sensitive to odour molecules with a less volatile, possibly more complex molecular structure than the odorants to which humans are sensitive (Wright and Smith, 2004). This sense is important in reproduction, allowing many animals to sense sexual attractant odours, or pheromones, thus governing 'mating behavior'. It is also used by reptilian and mammalian predators in tracking their prey (Ache and Yong, 2005).

Olfactory memory

Olfactory memory refers to the recollection of odors. Studies have found the various characteristics of common memories are same for odor memory including persistence and high resistance to interference. Explicit memory is typically the form focused on in the studies of olfactory memory, though implicit forms of memory certainly supply distinct contributions to the understanding of odors and memories of them. Research has demonstrated that the changes to the olfactory bulb and main olfactory system following birth are extremely important and influential for maternal behavior. Mammalian olfactory cues play an important role in the coordination of the mother infant bond and the following normal development of the offspring. Maternal breast odors are individually distinctive and provide a basis for recognition of the mother by her offspring.

Olfactory memory was developed throughout evolution for various reasons. Among the most notable reasons are those related to the survival of the species and the development of early communication. Even in humans and animals today, these survival and communication aspects are still functioning. There is also evidence suggesting that there are deficits in olfactory memory in individuals with brain degenerative diseases such as Alzheimer's disease (Bahuleyan and Singh, 2012) and dementia (Buchsbaum et al., 1991). These individuals lose the ability to distinguish smells as their disease worsens. There is also a research showing that deficits in

olfactory memory can act as a base in assessing certain types of mental disorders such as depression as each mental disorder has its own distinct pattern of olfactory deficits (Wu et al., 1993).

Conclusion

In this review article, the physiology of olfaction under various headings was discussed. Olfaction as a special sense not only helps in the day to day activities but it influences the social behavior of an individual. Thus, it needs special attention. Although many studies have been undertaken to bring out the whole molecular mechanism of olfaction, certain areas are still untouched and require additional researches in the future to disclose the unknown enigma in the field of Physiology.

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Conflict of interest

The authors have declared no conflict of interest.

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