Neuroanatomy and Neurophysiology of the Olfactory Signal Transduction Pathway

Melissa Singletary and Samantha Hagerty

Abstract

The sense of olfaction is surprisingly influential in many areas of the central nervous system that seem unrelated to how something smells. Perception of different odors can influence numerous biological functions: from reproduction to social interactions. Olfaction abnormalities have also been associated with various psychological conditions in humans, such as major depressive disorder and neurodegenerative diseases. This broad range of olfactory influence is giving researchers a new appreciation for the importance of sensory system. It is also unique in both neural organization and the environmental challenges that come from direct exposure of neurons to the external environment. This chapter will focus on predominantly the mammalian neuroanatomy and neurophysiology of the olfactory signal transduction pathway, with highlights on canine-specific attributes.

Keywords

Olfactory signal transduction • Olfactory neurophysiology • Olfactory neuroanatomy • Central olfactory pathway

M. Singletary (✉)
Canine Performance Science, Auburn University College of Veterinary Medicine, Al 36849 Auburn, US
e-mail: mas0028@auburn.edu

M. Singletary · S. Hagerty
Department of Anatomy, Physiology and Pharmacology, Auburn University College of Veterinary Medicine, Al 36849 Auburn, US

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1 Olfactory Signal Transduction Pathway: Peripheral Nervous System

Olfactory receptors (OR) are chemosensory G-protein coupled receptors (GPCR) with three distinct, or heterotrimeric, G-proteins including alpha, beta, and gamma subunits. They represent the largest multi-gene receptor repertoire in mammalian genomes (Buck and Axel 1991a, b). While the repertoire of OR genes varies by species, the relative abundance in comparison to other receptor families is conserved across mammalian genomes. Olfactory sensory neurons (OSN) and Bowman's glands are the two main components that differentiate the areas of olfactory neuroepithelium from respiratory epithelia in the nasal cavity. At the apical surface, dendritic processes of an OSN are densely packed with approximately 1–50 non-motile cilia (Morrison and Costanzo 1990). The cilia express the classic 9 + 2 configuration, which is 9 pairs of microtubule doublets arranged in a concentric ring around a central pair of microtubules in the proximal segment but tapers to microtubule singlets more distally (Menco 1984; Williams et al. 2014). Though this configuration is typical of motile cilia, the OSN cilia are non-motile due to a lack of dynein arms. The heavy density of OR and signaling proteins are preferentially localized in the more distal end of the cilia where improved chance of stimulus interaction can occur (Menco 1984; Matsuzaki et al. 1999; Flannery et al. 2006; Jenkins et al. 2009), potentially increasing the sensitivity of odor detection.

A basic principle on which the olfactory system functions is the expression of only one receptor type on a given OSN also referred to as the one-receptor-one-neuron rule (Li et al. 2004). This monoallelic and monogenic expression provides stimulus specificity and discrimination. Odorants engage with these OR with varying degrees of affinity, setting off a cascade of enzymatic events (Buck and Axel 1991a, b; Firestein 2001).

The summation of potentials when multiple ORs are stimulated by the same odorant type result in an action potential when the threshold is reached (Firestein 2001). The combinatorial coding at the OR level is achieved by specific ORs being capable of odorant detection in a narrow spectrum or a broad spectrum while a specific odorant molecule can also activate a variety of ORs across a spectrum of intensity and attraction. The variations of OR sensitivity and specificity result in groups of odorant-specific activation that can be overlapping and allow for a more considerable combinatorial coding for more odorant detection possibilities (Persuy et al. 2015).

Odor intensity is directly influenced by odor concentration, which subsequently may correlate to the number of OSN stimulated, though conflating factors such as exposure duration or physiological state may limit interpretation as a solely linear relationship (Stevens 1960; Chastrette et al. 1998; Sirotin et al. 2015). There is a wide range of receptor tuning widths, described as the average number of activated glomeruli per single odorant, and non-linear responses to monomolecular, binary, similar molecular groups or complex odor mixtures. In mice, studies showed increased complexity from binary mixture to more complex odor mixtures involved increasing levels of antagonistic odor interactions (Zak et al. 2020). At

the odorant–receptor interface, the series of molecular mechanisms involved in odorant recognition by the receptor is not yet fully defined. The subsequent signal cascade following receptor activation and cellular depolarization is better studied and established.

As with other electrically excitable cells, the intracellular environment of OSN is negative compared to the exterior space, though the unique characteristic of being exposed to the external environment requires these neurons to actively maintain a state of excitability under less than ideal conditions. The resting membrane potential of OSN that remain in holding states primed for activation is -65 mV with an activation threshold of approximately -45 mV (Firestein 2001). OR activation is initiated when the proper odorant ligand reaches the binding pocket of an appropriate GPCR, resulting in a conformational change in the heterotrimeric G-protein, G_{olf}, and guanine nucleotide exchange of GDP for GTP. This exchange prompts dissociation of the alpha subunit, $G_{\alpha olf,}$ from G_{β} and G_{γ} subunits. Specific sub-molecular events resulting in recognition and activation at the odorant-receptor interface are not fully elucidated, as several theories associated with vibrational, molecular, and biochemical properties are still explored yet not universally agreed upon (Turin 2002; Block et al. 2015; Hoehn et al. 2017). The considerable representation of OR among the mammalian gene repertoire emphasizes its evolutionary conservation and biological relevance (Buck and Axel 1991a, b). A characteristic of GPCR class receptors is the seven-transmembrane weaving pattern between intra and extracellular sides of the plasma membrane. Starting with an intracellular C-terminus, the protein transverses the membrane 7 times in loops leading to an extracellular N-terminus. Upon the conformational change resulting in the release of the $G_{\alpha olf}$ subunit, this subunit then interacts with adenylyl cyclase III (ACIII) enzyme allowing for the intracellular conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) (Firestein 2001). Levels of cAMP increase to approximately 100 cAMP molecules per ACIII, allowing for cAMP molecules to bind to the transmembrane cyclic-nucleotide gated (CNG) ion channel which results in a conformational change and subsequent opening. CNG channel opening allows a selective influx of positively charged calcium (Ca^{2+}) and sodium (Na^{+}) into the cell. Concentration of CNG channels is estimated to exceed 2,000/μm^2, so the relative gradient change with incoming positive charge is considerable. The changing membrane potential is further facilitated by the opening of voltage-gated ion channels, specifically calcium-activated chloride channels, causing an efflux of negatively charged chloride (Cl^{-}) into the extracellular space (Firestein 2001). The opening of these voltage-gated ion channels is thought to occur via transmembrane protein TMEM16B, which are suggested to associate with the calcium-calmodulin precursor, calcium-free calmodulin apocalmodulin (apoCaM), under resting conditions (Yang et al. 2014). The combination of positive influx and negative outflux may allow for more rapid membrane depolarization as well as an environmental buffer to maintain proper resting states in less controlled conditions. As OSN are exposed to the external environment in the nasal cavity, the cilia on which the receptor sites are embedded may be more vulnerable to atypical extracellular ion concentrations through external environmental

perturbations. Therefore, this dual ion buffer system allows for a unique fail-safe aiding in depolarization even when extracellular sodium levels may be low. As an electrically excitable cell, the high intracellular chloride concentration compared to the exterior environment is maintained as a mechanism for quick membrane potential depolarization (Firestein 2001). Chloride efflux has been reported to represent 80% of the primary depolarization in the OSN (Lowe and Gold 1993). The re-establishment of this Cl^- gradient is unsurprisingly critical in maintaining a buffer, and more recent work indicates ion transporter NKCC1as the main contributor (Haering et al. 2015). The NKCC1 ion transporter is a sodium, potassium, chloride symporter transporting in a 1:1:2 ratio, respectively (Haering et al. 2015). Redistribution of the cytosolic calcium to the extracellular space is also carried out by Na^+/ Ca^{2+} extrusion through the transporter NCKX4 (Stephan et al. 2012). The gradient re-establishment, or repolarization phase, initiates with temporary hyperpolarization in which the cell is unable to respond to a stimulus while membrane potential gradient is resetting.

There are several internal feedback mechanisms at play throughout this molecular cascade involving multiple ion channels. Calcium influx during depolarization acts directly on the associated ion channels through calcium-calmodulin binding, decreasing the ion channel sensitivity to cAMP and dampening the response, which elevates the threshold stimulus intensity required for subsequent excitation. Additionally, the regulator of G-protein signaling (RGS) reduces levels of cAMP production by direct inhibition of adenylyl cyclase III activity. Supporting evidence of this was demonstrated through experimental inhibition of RGS2, resulting in downregulation of signal transduction in the neuronal membrane (Sinnarajah et al. 2001). A similar multi-modal approach for response modulation to olfactory stimuli is seen in regulation of adaptation by adjusting OSN sensitivity (Kurahashi and Menini 1997; Reisert and Matthews 2000; Firestein 2001). Increased levels of cAMP by ACIII activate phosphokinase A (PKA), which phosphorylates the receptor, thereby inhibiting its continued function. Simultaneous action by odorant receptor kinase (ORK) functions through cAMP activation of the G-protein beta-gamma subunits. Furthermore, calcium-calmodulin activates phosphodiesterase (PDE) within the cytoplasm, which degrades cAMP to restore baseline levels (Firestein 2001). More recently, olfactory marker protein (OMP), generally considered a biomarker for neuronal maturity in OSN, has been implicated in modulation of the basal cAMP levels (Dibattista and Reisert 2016). OMP is not expressed in basal stem cells or developing OSN found in the lower region of OE but is present when functional activity is reached, which takes approximately one week in regenerating OSN (Kondo et al. 2010; Savya et al. 2019). The achievement of functional activity would be consistent with the ability to regulate and restore membrane potential, which is required for successful cell signaling.

Generated action potentials propagate through the basally extended axon where it terminates at a monosynaptic second neuron target in the olfactory bulb (OB). The OSN utilizes glutamate as its primary excitatory neurotransmitter for signal communication (Berkowicz et al. 1994). The OSN axons will functionally collate with similar OR expression and bundle into fascicles enwrapped in olfactory

ensheathing cells (OEC) and traverse through the cribriform plate to enter the central nervous system.

2 Olfactory Signal Transduction Pathway: Central Nervous System

As first-order neurons, the OSN axons project from their soma within the olfactory epithelium to functionally respective glomeruli within the OB on second-order neurons. The various glomeruli are selective for individual OR genes allowing for collections of OSN axons expressing the same OR to bundle as axon fascicles and innervate selective glomeruli within the OB, passing along the signal from peripheral nervous system into the central nervous system (CNS) (Zhu et al. 2022). The OB will serve as the initial filter within the CNS aiding in discrimination, selectivity, and modification of odor sensitivities through modulation of odor noise (Jia et al. 2014).

There is significant variability in relative olfactory bulb size within the CNS across species. Some species show significantly larger relative bulb size, such as the shark and the dog, than other species such as humans. The OB volume for the dog was reported to be 0.18 ± 0.02 cm^3 while the humans' was 0.06 ± 0.01 cm^3 (Kavoi and Jameela 2011). The major cellular components of the olfactory bulb include mitral and tufted cell neurons, peri-glomerular cells, and granular cells. The site of synaptic connectivity between first-order OSN and second-order OB neurons occurs in the glomeruli of the glomerular layer. As many different OSN expressing individual OR alleles converge at shared glomeruli, there is significant input from the neuroepithelial level at these synaptic sites. In rabbit models, there are approximately 25,000 axons per glomeruli and about 1,800 glomeruli per olfactory bulb (Firestein 2001). The olfactory bulb can be divided into six distinct layers that are categorized based on cell types present and, particularly, where the cell bodies of such cells are located. OB glomeruli represent spatially encoded regions of incoming olfactory information as well as secondary processing for further projections. The basic OB divisions are olfactory nerve, glomerular, external plexiform, mitral cell plexiform, internal plexiform, and granule cell layers. First, the olfactory nerve layer is where OSN axonal projections enter the olfactory bulb with information obtained from the nasal epithelium. The second, termed glomerular layer, is the synaptic site where OSN release neurotransmitters for post-synaptic excitation by secondary neurons. These neurons are collectively called juxtaglomerular cells but are further subcategorized into periglomerular cells, external tufted cells, and superficial short-axon cells. The third layer is called the external plexiform layer, where primarily dendrodendritic synapses and tufted cells are found. The fourth, or mitral cell layer, as the terminology suggests is where mitral cell bodies are found although their dendritic processes extend to the glomeruli for OSN convergence. Next, the internal plexiform layer is characterized by little synaptic activity and few cells, through which axons from mitral or

tufted cells pass. The innermost layer is known as the granular layer, where granular interneuron cells of the OB core function as stem cells (Sarnat and Yu 2016; Sarnat and Flores-Sarnat 2017; Sarnat et al. 2017).

The monoallelic and monogenic neuron expression also relates to associated specific receptor glomeruli. Located on the superficial layer of the olfactory bulb, these spherical glomeruli serve as the synaptic site between OSN axons and mitral and tufted cells. Mitral cells are the primary efferent projection cell that are also thought to play a role in post-synaptic signal modification, while tufted cells are also involved in signal reception and projection. Both are considered glutaminergic neurons as the excitatory neurotransmitter used is glutamate. Thousands of OR-specific olfactory sensory neurons terminate on a single glomerulus, with approximately 50 mitral and tufted cells involved in the post-synaptic response. Maturation of the olfactory bulb results in mitral neuron cell developmental changes, suggested by the increasing size of mitral cells with corresponding decrease in quantity from juvenile age to adulthood (Wei et al. 2008). Lateral interconnected mitral cells "refine" or "modify" the signal. This is thought to also be a mechanism to support discrimination of odors. Glomeruli are surrounded by periglomerular cells, which are interneurons that form dendrodendritic synapses between the olfactory signal-carrying neurons and associated cells, mainly for inhibitory purposes. Periglomerular cells consist primarily of inhibitory gabaminergic and dopaminergic neurons acting on NMDA receptors of the mitral and tufted projection cells within and between glomeruli (Ohm et al. 1990, 1991). The granular interneuron cells inhabiting the innermost layer also share inhibitory roles regulating mitral and tufted cells through dendrodendritic gabaminergic synapses (Hirata et al. 2006). An inverse reciprocal relationship between mitral and granular cells is evident, in which mitral to granular stimulation is excitatory while granular to mitral stimulation is inhibitory (Kosaka et al. 1985). An estimated 50–100 inhibitory granular cells are reported to interact with a given mitral cell (Hirata et al. 2006). Within the central nervous system, the olfactory bulb has the most robust presence of dendrodendritic synapses (Kaba and Keverne 1992; Hayashi 1999). Not only the OB size but also activity vary between species. Some studies in the dog have suggested that female dogs have more active olfactory bulbs and a suggested stronger long-term odor memory than those of males (Wei et al. 2017). This signal transduction pathway from first-order to second-order neuron has remained ipsilateral to the point of the OB. Post-OB the pathway complexity increases and is less well characterized with cross-over and extensive connections throughout the brain.

Olfactory signal information continues from olfactory bulb glomerular convergence through second-order neurons into the olfactory peduncle via the lateral olfactory tract and then into primary cortical olfactory areas. These areas include the basilar forebrain, limbic system, piriform lobe, lateral olfactory and parahippocampal gyri, anterior olfactory cortex, periamygdala, entorhinal cortex, and anterior cingulate cortex (Brunjes et al. 2011; Jia et al. 2014, 2016; Uemura 2015). From an evolutionary perspective, the limbic system that includes the OB, entorhinal cortex, hippocampus, and amygdala is generally considered a more primitive

region of the brain associated with emotions and memories, which is relevant as it relates to olfactory processing (Kanter and Haberly 1990). The olfactory cortex consists of the anterior olfactory nucleus (AON), the tenia tecta, the olfactory tubercle (OT), the piriform cortex (PC), cortical amygdaloid nucleus, periamygdaloid cortex, and the entorhinal cortex (Price et al. 1991; Zelano and Sobel 2005). Signal processing occurs in the piriform cortex, where primary processing and assigning contextual information of odor sources is thought to occur (Haberly 2001). Conscious perception of the odor source may occur in the frontal lobe area of the neocortex (Ongur and Price 2000). More recent research using tandem diffusion tensor imaging (DTI) and the Klingler dissection method olfactory cortex network mapping in dogs revealed an extensive pathway to the occipital lobe in addition to the established cortical spinal tract, limbic system, piriform lobe, and entorhinal pathways (Andrews et al. 2022). The mapping and coding information from the OB is not retained within the piriform cortex, but rather has more plasticity. With repeated or varying exposures of odorants and odorant mixtures, the higher cognitive response has been shown to change and demonstrate plasticity that may result in unique odor perceptions under varying conditions. The trigeminal system engages with the olfactory pathway, providing ancillary information through odor activation of trigeminal sensory receptors producing somatic sensations related to temperature and nociception. This trigeminal activation can directly influence airflow and has even been shown to activate the piriform cortex (Hummel and Frasnelli 2019). Quantity and quality of odors are important to optimize olfactory perception, though there is much to learn about the complex neuroprocessing of odors.

Much of the projections throughout the brain are confined respectively through ipsilateral hemispheric communication, but there are contralateral communications that cross-over. Functional asymmetry in hemispheric processing of various information and associated behaviors has been noted across multiple species (Gunturkun et al. 2020; Vallortigara and Rogers 2020). There are suggestions that olfactory processing also is impacted by lateralization with detection, discrimination, and identification being differentially processed between the left and right hemispheres (Cavelius et al. 2022).

The AON is the most rostral region of the olfactory cortex (OC) and has a large number of commissural fibers that project contralateral and ipsilateral information to the piriform cortices (PC) (Brunjes et al. 2005; Zelano and Sobel 2005; Yan et al. 2008). The anterior commissure is one of two major regions of the brain where pathways for transfer of information between hemispheres occur. Olfactory allocortical structures transfer information across the midline at the anterior commissure. The average dog brain is 74600 mm^3 with the anterior commissure area representing 2.54 mm^2 (Ashwell 2016).

The olfactory sensory system does communicate with the thalamus but uniquely does not require communication with the thalamus as an intermediary prior to higher brain centers and has a direct connection to those areas (Ongur and Price 2000; Shepherd 2005; Kay and Sherman 2007). All other sensory systems require thalamocortical processing, but in regards to olfaction the thalamus is thought to

hold a role in odor threshold (Challis et al. 2015). This direct connection to higher cortical areas is thought to contribute to the strength of odor-associated memories. Studies have suggested that the olfactory bulb cortex functions in a similar capacity to the sensory processing in the thalamus (Zelano and Sobel 2005; Sarnat and Flores-Sarnat 2017; Sarnat et al. 2017). Most OB output is carried toward the PC, where signals are projected to the dorsomedial nucleus of the thalamus, orbitofrontal cortex, and may have signal regulatory feedback roles as discussed in the OB. In contrast to the elaborate topographical spatial patterns found in the OB divisions, the PC is far less organized. Although there are three distinct layers, they appear highly associative without specific signal projections to particular target cells (Miyamichi et al. 2011; Wiegand et al. 2011). The entorhinal cortex receives input from multiple areas of the olfactory tract and connects to the hippocampus, so it is considered relevant in associating olfactory information with memories (Zelano and Sobel 2005). The amygdala, part of the limbic system, sends inputs into the hypothalamus while also feeding back onto the OB. This olfactory cortex region is thought to play a role in assigning emotion to odor profiles (Zelano and Sobel 2005; Good and Sullivan 2015). Among the olfactory cortex, the only region not known to directly feedback to the OB is the olfactory tubercle. The olfactory tubercle communicates with the dorsomedial thalamic nucleus as well as with the nucleus accumbens, ventral tegmentum, and pallidum which are thought to be the association of reward and motivation in olfaction (Heimer 2003; Ikemoto 2007). In dogs that perform odor-based detection tasks, the reward–behavior associations with the olfactory system include the caudate nucleus, the entorhinal cortex, and hippocampus related to development of odor memory, and emotional or motivational associations linked to the amygdala (Herrick 1933; Schoenbaum et al. 1999; Haberly 2001; Gottfried 2010; Wilson and Baietto 2011; Wilson and Sullivan 2011).

The olfactory cortex is so richly connected to other areas in the brain and many of these connections not only receive information but provide information to the olfactory sensory system as part of a feedback loop (Kay et al. 1996; Wilson 1998a, b; Zufall and Leinders-Zufall 2000). Feedback mechanisms from the olfactory and orbitofrontal cortex to the OB are thought to function as sources of adaptation and habituation. The source of adaptation can be either peripheral or central. Peripheral adaptation involves a decreased neural response in the pre-glomerular tract while central adaptation is characterized by a reduction in post-glomerular tract neural responses (Pellegrino et al. 2017). While the source of adaptation is mainly sensory fatigue, habituation is considered a reduced behavioral response resulting from repeated stimulation (Rankin et al. 2009). The collective phenomena have been further overlapped in some descriptions of adaptation as the neural basis of behavior response of habituation (Pellegrino et al. 2017). This adaptation can occur after as little as two repetitions of an intense odor stimulus where perception is diminished though the electrical activity at the OSN level is not necessarily diminished (Hummel et al. 1996; Hummel et al. 2006).

The multidimensional nature of this sense perceives odors that may have positive or negative hedonic value (the measure of pleasantness), may be repulsive or share in activation of the trigeminal system and may be the carrier of a biologically important message. As a primary sensory system for the dog, their behavior is significantly influenced by olfactory inputs processed in higher cortical areas (Siniscalchi 2016; Siniscalchi et al. 2016).

Various methods are used to evaluate neuroanatomical and functional neurophysiological processing including positron emission tomography scanning and functional magnetic resonance imaging (fMRI). The use of extensive training methods in dogs allows for voluntarily fMRI scans while awake and unrestrained (Karl et al. 2019; Strassberg et al. in press), allowing more research to explore the functional neurophysiological and cognitive processes. The limitations to these studies are the time and expense of maintaining a trained cohort of dogs for voluntary awake scanning to achieve biologically relevant scans that are unhindered by restraints or anesthesia, which can alter cognitive states and functional interpretation of the results (Thompkins 2016; Thompkins et al. 2016). One of the pioneer studies to scan awake unrestrained dogs showed the primary areas of the brain involved in odor processing, which included the OB and the olfactory cortex, were activated in both awake and anesthetized states at varying degrees, though higher cortical regions were seen predominantly in the awake state (Jia et al. 2014). As these higher cortical regions are involved in perception and identification through odor detection, discrimination, learning, and memory, this finding is consistent that an awake and alert state is necessary for maximal olfactory pathway activation (Siniscalchi 2016; Siniscalchi et al. 2016).

The superior behavioral olfactory acuity of macrosmatic species is attributable to multi-factorial traits. In the dog, there are a number of collective anatomical and physiological features that include skull nasal vestibule depth increasing odorant time of flight (Craven et al. 2010), larger total surface area of the olfactory neuroepithelium (Sjaastad et al. 2010), a dedicated olfactory recess for odorant processing (Craven et al. 2004), a greater number of functional odorant receptor genes with lower pseudogenization rate (Quignon et al. 2003; Olender et al. 2004), a higher density of olfactory sensory neurons present in the olfactory epithelium (Uemura 2015), a higher density of cilia present per olfactory sensory neuron (Uemura 2015), and an increase in OB volume relevant to the total brain weight (Reep et al. 2007; Kavoi and Jameela 2011; Uemura 2015). These unique features have positioned dogs as an excellent tool for uncovering the capacity and complexity of odor processing in mammals and a translational model for informing the underlying principles of odor learning and behavior.

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