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Chapter

Introductory Chapter: Dysfunction of the Olfactory System and Nasal Disorders

Thomas Heinbockel and Balwant S. Gendeh

1. Introduction

Our sensory systems are continuously exposed to external stimuli that are processed in the neural pathways of the nervous system in order to maintain bodily homeostasis and to provide appropriate behavioral responses. While some of our senses are more readily recognized for their role in guiding our daily lives and routine behaviors, such as vision and hearing, other senses are noticed primarily when they fail to work or are impaired during disease. This is the case for our chemical senses, taste and smell [1]. Recent estimates suggest that more than 12% of the U.S. population experiences taste or smell (chemosensory) dysfunction [2, 3]. Therefore, it is critical to identify treatments for smell and taste disorders [4]. Olfaction is increasingly acknowledged for its predictive value as an indicator of disorders. Olfactory deficits are evident early on in certain disorders such as Alzheimer's Disease and Parkinson's Disease. More generally, olfactory dysfunction is found in diseases that cause degenerative neuropathology, progressive loss of memory and communication function, normal age-based decline of physiological functions, intellectual challenges, depressive and anxiety disorders, as well as post-traumatic stress disorders. The relevance of olfaction as a predictor of disease has come to the forefront during the Covid-19 pandemic. Many Covid-19 patients experience smell and taste dysfunctions that are not related to blockage of nasal passages as seen in the upper respiratory tract infections [5–8].

2. The olfactory epithelium

This chapter briefly introduces the structures and functions of the nose and olfactory pathway since they form the basis of dysfunctions of the olfactory system and nasal disorders. The nasal passages start with the nostrils or nares separated by a septum. The nasal passages include the vestibule which is the most anterior part of the nasal cavity. The nasal cavity is enclosed by an elastic cartilage and lined by a stratified squamous, keratinized epithelium. The back part of the nasal cavity is lined by the respiratory epithelium, which is a pseudostratified, ciliated, and columnar epithelium. Likewise, this respiratory epithelium is found further down the airways including the trachea and bronchi. Our organ of smell is a specialized epithelium, the olfactory epithelium, which is also a pseudostratified, ciliated, and columnar epithelium. This epithelium covers the superior nasal concha and presents as the olfactory area. Each nasal cavity has an olfactory area in the roof of the nose. The term olfactory mucosa describes the olfactory epithelium and the underlying connective tissue (lamina propria). The olfactory mucosa contains several

cell types. The olfactory receptor cells in the epithelium are bipolar nerve cells. Their oval nuclei are located in the central one third of the olfactory epithelium. These cells detect smell [9]. The axons of olfactory receptor cells form the olfactory nerve, cranial nerve I. The axons traverse the cribriform plate of the ethmoid bone and project to the ipsilateral olfactory bulb where they target central neurons. Olfactory receptor cells are surrounded and cushioned by the supporting cells. The supporting cells (sustentacular cells) have their nuclei in the upper one third of the epithelium. They have cigar-shaped, elongated nuclei. Olfactory receptor cells are equipped with radiating cilia, whereas the supporting cells have microvilli at their apical surface. The basal cells have their nuclei in the lower one third of the epithelium at the base of the epithelium. They are precursor cells and actively divide after birth to replace olfactory receptor cells. The life span of olfactory receptor cells is 30–60 days. They undergo continuous replacement through the basal stem cell population [10]. Bowman's glands in the connective tissue secrete mucus to prevent constant olfactory stimulation. Bowman's glands have a duct to the surface of the olfactory epithelium. Their secretion produces a fluid environment around the olfactory cilia and may clear the cilia, facilitating the access of new odor substances. In addition, the mucus creates the ionic milieu around the cilia and contains an odorant-binding protein to trap odorants and to bring them to cilia.

The olfactory epithelium in the nose is part of the respiratory system. The primary function of the respiratory system is respiration, that is, the system provides the gas exchange between air and blood, so blood becomes oxygenated. The part of the system involved in gas exchange is the lungs. Another part of the system is a branching system of airways that brings air to and from lungs via the respiratory movements of thoracic walls and diaphragm. This part carries out a second function of the system, which is a somewhat minor function, namely, it humidifies the air, cleans the air, and warms the air. It works more like an air-conditioning system. Along the same line, we can divide the system into two principal regions. The conducting portion includes the parts of the respiratory system that are responsible for supplying the lungs with air: nasal cavities with olfactory areas, nasopharynx, larynx and epiglottis, trachea, bronchi, bronchioles, and terminal bronchioles. The respiratory portion is the site of gas exchange and includes the respiratory bronchioles, alveolar ducts and sacs, and alveoli. The olfactory epithelium is much thicker than the respiratory epithelium, which is found in the nose and the respiratory tract, whereas the olfactory epithelium is found only on the roof of nasal cavity. The respiratory epithelium contains goblet cells that secret a mucus which covers the epithelium and traps dust particles. Goblet cells are absent from the olfactory epithelium.

3. Olfactory receptor cells and transduction

Olfactory receptor cells have a distinct dendritic process that extends to the surface of the epithelium where its tip is expanded into a club-shaped prominence, the olfactory vesicle. This bears cilia, which have the typical 9 + 2 microtubule arrangement for some of their length, but there is a long distal portion, which contains only the two central microtubule fibers. In contrast to cilia in the respiratory epithelium, the olfactory cilia (5–20) are almost immotile, and they are inserted into basal bodies in the olfactory vesicle. It is in the cilia of olfactory receptor cells where olfactory transduction takes place, that is, the conversion of an odor signal into an electrical signal. Odorant molecules bind to olfactory receptor proteins and trigger a signaling cascade that involves G-proteins and leads to the generation of action potentials (nerve impulses). These nerve impulses are sent to the brain, specifically, to the olfactory bulb.

All olfactory receptor proteins are part of a family of G-protein-coupled receptors that are expressed in the olfactory epithelium [11–13]. There are many different odor receptor proteins and genes that encode them, with more than 1000 in the mammalian genome. Not all of these potential odor receptor genes are expressed and functional. The olfactory receptor multigene family consists of around 400 genes in humans and 1400 genes in mice [14–17]. According to an analysis of data derived from the Human Genome Project, humans have approximately 400 functional genes coding for olfactory receptors, and about 600 candidates are pseudogenes [14]. It implies that a human nose has around 400 types of scent receptors or ~ 400 different functional olfactory receptors. This is a large number since the entire human genome has only ~20,000–25,000 genes. It implies that ~2% of our genes are coding for olfactory receptors. Each olfactory receptor cell in the olfactory epithelium expresses only one of these 1000 olfactory receptor genes [18]. The expression of olfactory receptor genes is confined to four different zones of the olfactory epithelium [19–21]. Olfactory receptor cells that express the same olfactory receptor are found in only one of the four zones and they project to the same glomerulus in the olfactory bulb. The cells are randomly distributed in a given zone.

Olfactory receptor cells respond to several different odor-causing chemicals. Each receptor cell type can respond to more than one odorant. A given odorant can activate one or more receptor cells. Different types of receptor cells can respond not only to the same but also to different odorants. When an odorant ligand binds to a receptor protein, these proteins initiate a G-protein mechanism, which uses cyclic AMP (cAMP) or inositol triphosphate (IP3) as a second messenger [22]. The intracellular messengers open sodium and calcium channels, which results in depolarization of the receptor membrane that then triggers an action potential.

4. The olfactory pathway

The olfactory pathway starts with olfactory receptor neurons in the olfactory epithelium that send their axons to the ipsilateral olfactory bulb. There, they make synaptic contacts with central neurons in spherical structures, the olfactory glomeruli (2000 per bulb in the mouse). In the olfactory bulb, sensory information is processed in olfactory glomeruli. Each glomerulus is a discrete anatomical and functional unit and serves as an anatomical address dedicated to collecting and processing of specific molecular features about the olfactory environment conveyed to it by olfactory receptor cell axons expressing specific olfactory receptor proteins [23–25]. Thus, the glomeruli in the olfactory bulbs are organized chemotopically [26, 27], analogous to visuotopy, in visual systems, and tonotopy, in auditory systems. Olfactory information is extensively processed at the level of the glomeruli through feedforward and feedback inhibition and modulation provided by centrifugal neurons. Information is subsequently conveyed to higher-order olfactory center such as the olfactory cortex in vertebrates.

Olfactory receptor cells in the olfactory epithelium that have the same type of olfactory receptor, that is, they express the same olfactory receptor gene (1 of ~1000), send their axons to the same glomerulus (1 of 2000) in the olfactory bulb. This is an example of sensory axons converging on one glomerulus in the brain. In the olfactory bulb, olfactory receptor cell axons synapse on mitral/tufted cells. Glomerular mitral/tufted cells process odor signals coming from the nasal olfactory epithelium. The central neurons in the olfactory bulb, such as the mitral and tufted cells, project to higher olfactory centers. Twenty to 50 neurons output neurons (mitral/tufted cells), innervate each glomerulus, and project out of the olfactory bulb. Mitral cells that innervate different glomeruli typically respond to different types of odorants. A given odorant can activate mitral cells in several or many glomeruli. Odorant identity

can be encoded through a combination of olfactory receptors, where each olfactory receptor detects one molecular feature of the odorant. Mitral and tufted cells send their axons through the lateral olfactory tract to the olfactory cortex, which includes the anterior olfactory nucleus, the piriform cortex, parts of the amygdala, the olfactory tubercle, and parts of the entorhinal cortex. From the amygdala, olfactory information is passed on to the hypothalamus and from the entorhinal cortex to the hippocampus. Olfactory information can be sent to the orbitofrontal cortex through the thalamus from olfactory cortical areas, except the anterior olfactory nucleus. Centrifugal fibers that originate outside of the olfactory bulb project to the olfactory bulb from the basal forebrain (horizontal limb of the diagonal band) and midbrain (locus coeruleus and raphe). The functional significance is a possible modulation of olfactory processing during different behavioral states.

Olfactory disorders and dysfunctions have received attention because they can result in serious problems, such as our inability to smell warning odors (fire, gas) and an impaired ability to taste food through retronasal stimulation of olfactory receptors [3]. Anosmia (loss of smell) and hyposmia (diminished smell) result from a number of etiologies. Specific anosmia refers to lowered sensitivity to a specific odorant and general anosmia denotes complete lack of olfactory sensation. Dysosmia (distorted smell) and phantosmia (phantom smells) may accompany these conditions. Cacosmia refers to olfactory hallucinations of repugnant smells.

5. Olfaction and gustation

Olfaction and gustation are our chemical senses and share a number of similarities and differences. Both senses extract information from the chemical stimuli in the environment, respond to a wide array of chemicals, and use G-protein-coupled receptors. However, in taste, this transduction mechanism is limited to sweet, bitter, and umami, whereas salty and sour use other signaling mechanisms. Receptor cells in olfaction and gustation show strong adaptation during continued stimulation and they undergo turnover and replacement throughout life. Both chemical senses provide important information for our survival and play a role in food selection and protect us from ingesting toxins. One difference between the two sensory systems is the fact that olfactory receptor cells are neurons and taste receptor cells are modified epithelial cells. Our understanding of the coding of taste qualities is better than that of odor quality. While olfactory stimuli evoke many sensations, no clear odor qualities have been described. The success of the perfume industry tells about the importance of olfactory stimuli as social cues.

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Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this chapter.

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