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Review

Peripheral modulation of smell: Fact or fiction?

Mary T. Lucero*

Department of Physiology, School of Medicine, University of Utah, 420 Chipeta Way Ste, 1700 Salt Lake City, UT 84108, United States

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ABSTRACT

Despite studies dating back 30 or more years showing modulation of odorant responses at the level of the olfactory epithelium, most descriptions of the olfactory system infer that odorant signals make their way from detection by cilia on olfactory sensory neurons to the olfactory bulb unaltered. Recent identification of multiple subtypes of microvillar cells and identification of neuropeptide and neurotransmitter expression in the olfactory mucosa add to the growing body of literature for peripheral modulation in the sense of smell. Complex mechanisms including perireceptor events, modulation of sniff rates, and changes in the properties of sensory neurons match the sensitivity of olfactory sensory neurons to the external odorant environment, internal nutritional status, reproductive status, and levels of arousal or stress. By furthering our understanding of the players mediating peripheral olfaction, we may open the door to novel approaches for modulating the sense of smell in both health and disease.

Contents

1. Introduction

The emotional, reproductive, circadian, nutritional, and external environmental states of an animal are constantly changing. Sensory input is matched to the internal needs and external environment through modulation at different levels of the processing pathway. It is widely accepted that at least some component of sensory modulation occurs at the level of the peripheral receptor cells in all sensory systems except for one—the olfactory system. The vast majority of publications on the olfactory system dismiss modulation of olfactory signals at the level of the olfactory epithelium. Instead, published reports often include such words as 'the olfactory bulb is the first level of processing in the olfactory system' (the olfactory bulb being the CNS

* Tel.: +1 801 585 5601.
E-mail address: mary.lucero@utah.edu

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target for axons from olfactory sensory neurons in the olfactory epithelium).

What is so different about olfaction that the scientific community clings to the notion that peripheral signals into the brain from olfactory sensory neurons is invariant while accepting peripheral modulation in other sensory systems? What is the evidence for peripheral modulation in the olfactory system? When is peripheral modulation of odor sensitivity brought into play? What mechanisms take place to modulate peripheral odor reception? Where are these mechanisms active in the olfactory epithelium? How does peripheral modulation affect behavioral responses to odors? Not all of these questions are easily addressed. However, recent progress in our understanding of peripheral modulation in olfaction suggests that it is time to rethink sensory processing in the olfactory system. The theme of this review is that new findings may lead to new strategies to advance our understanding of how internal and external signals impinge upon and modulate peripheral olfactory sensory processing.

2. Anatomy and physiology of the olfactory system

To understand the origin of the dogma that olfactory information processing occurs first in central nervous system circuits, and to put the studies that demonstrate peripheral sensory modulation into context, it is important to understand the anatomy and physiology of the olfactory system. There are a number of chemosensory structures in the nose that are related to olfaction, including the vomeronasal organ, septal organ, Grunenberg ganglia, and solitary chemoreceptors (reviewed in Ref. [1]). However, the following review will focus on the main olfactory epithelium of vertebrates. The olfactory mucosa is comprised of a pseudostratified neuroepithelium containing ciliated bipolar sensory neurons, microvillar cells, glial-like sustentacular cells, duct cells, neuronal progenitor cells, and basal stem cells (Fig. 1A). A basement membrane separates the epithelium from the glands, olfactory nerve bundles, and extrinsic innervation of the submucosa or lamina propria. Like most epithelia, the olfactory neuroepithelium is avascular. However, a rich vascular bed lies just below the basement membrane (Fig. 1B).

2.1. How are odors transduced?

Odorants bind to G protein-coupled odorant receptors (ORs) localized to the long slender cilia that extend from the apical dendritic knobs of olfactory sensory neurons into the mucus covering the nasal cavity [2]. According to the canonical model for olfactory transduction, odorants binding to specific odorant receptors activate a transduction cascade that includes activation of the olfactory specific G_{olf} [3], the alpha subunit of which increases activity of an olfactory specific adenylate cyclase III [4,5] in the cilia. Activation of adenylate cyclase III increases cAMP production. Cyclic nucleotide gated ion channels [6], also present in the olfactory cilia, bind intracellular cAMP, open, and allow a rapid influx of Na^+ and Ca^{2+}. Influx of these cations generates a depolarizing receptor potential. Moreover, the influx of Ca^{2+} in particular opens Ca^{2+}-dependent Cl^- channels, further depolarizing the cilia by allowing the efflux of anions (Cl^-). Ca^{2+}-activated Cl^- efflux may be less important in mammals than in fresh water aquatic animals [7]. If the odorant-generated receptor potential in the cilia is sufficiently large, it will trigger action potentials in the soma. Impulses are propagated along the unmyelinated axons of olfactory sensory neurons to their distant synaptic terminals in glomeruli in the olfactory bulb.

In addition to the canonical cAMP-based transduction pathway, there are subpopulations of sensory neurons that express other transduction proteins. These proteins include guanyl cyclase D, an enzyme present in certain olfactory sensory neurons and that responds to CO_2 [8]; or TRPM5-PLβ2 in olfactory sensory neurons that respond to social odorants [9]. Thus, within the population of vertebrate ciliated olfactory sensory neurons, there are subgroups of neurons that utilize different transduction pathways. These subgroups project to distinct regions of the olfactory bulb.

The termination of odorant responses in peripheral olfactory sensory neurons involves multiple steps including (a) removal of odorants from the air or mucus leading to unbinding from receptors; (b) degradation of cAMP [10]; (c) desensitization of CNG channels via Ca^{2+}-calmodulin [11]; and (d) rapid extrusion of Ca^{2+} via a Na^+/Ca^{2+} exchanger [12]. During prolonged odor stimulation, slow adaptation occurs in olfactory sensory neurons. Adaptation involves mechanisms including odorant receptor desensitization and activation of soluble guanylate cyclase by nitric oxide [13,14]. Activating soluble guanylate cyclase generates cGMP throughout the cell and this leads to a prolonged elevation of $[Ca^{2+}]_i$ [14] which, in turn, activates downstream enzymes that reduce odorant sensitivity. Pathways activated by odor stimulation and desensitization alike provide multiple substrates for modulation that could increase or decrease the output of olfactory sensory neurons.

2.2. How are different odorants perceived and discriminated?

The identification of odorant receptor genes [2] allowed molecular and genetic approaches to begin unraveling olfactory coding. Each olfactory sensory neuron expresses only one of the ~1000 odorant receptor genes found in rodents (~350 in humans). Each olfactory sensory neuron throughout the olfactory epithelium that expresses a particular receptor projects on average to 2 glomeruli in each one of the paired olfactory bulbs [15]. Conversely, each glomerulus in the main olfactory bulbs receives thousands of converging inputs from olfactory sensory neurons that all express the same odorant receptor. Thus, there is an exquisite targeting of odorant receptor specific axons onto glomeruli in the olfactory bulbs. Moreover, there is a loose chemotopic organization in the olfactory epithelium such that different classes of odorant receptors can be mapped to domains of glomeruli in the olfactory bulbs [16,17]. Because odorant receptors recognize specific features of odorant molecules, multiple odorants can bind to a single receptor with varying affinities. Conversely, multiple classes of receptors respond to the same odorant, again with varying affinities. In addition, because odors that we perceive as a single percept (e.g., the aroma of coffee) generally are a complex mixture of many different odorants, odors typically activate (or inhibit) multiple classes of odorant receptors [18–20]. The outcome is that odors are believed to generate a specific pattern of activity in thousands of olfactory sensory neurons that converge onto a particular collection of glomeruli in the olfactory bulbs and is encoded there by neurons that project to the olfactory (piriform) cortex and other brain centers including the amygdala and hypothalamus. Surprisingly, the odorant specificity of connections between the olfactory epithelium and the olfactory bulbs does not appear to be maintained at the higher cortical levels. Tracers injected into a single glomerulus in the olfactory bulbs are taken up by dendrites of projection neurons and transported to cortical neurons broadly distributed across the piriform cortex [21,22]. Modeling studies, combined with viral tracing and electrophysiological recordings, suggest that cortical representations of odors appear as sparsely distributed activity patterns. Furthermore, these patterns reflect extensive inhibitory processing and the convergence of inputs from multiple glomeruli [23,24]. In short, there is no obvious labeled-line coding of sensory information in olfaction. Understanding the central processing of olfactory information is an active area of investigation. New optogenetic tools that allow precise activation or inhibition of specific neuronal populations in behaving animals promise to greatly advance our comprehension of odor coding. Nonetheless, as new approaches are adopted