Review

Aging in the olfactory system

Arie S. Mobley[1], Diego J. Rodriguez-Gil[1], Fumiaki Imamura[1,3], and Charles A. Greer[1,2]

[1] Department of Neurosurgery, Yale University School of Medicine, New Haven, CT 06520, USA
[2] Department of Neurobiology, Yale University School of Medicine, New Haven, CT 06520, USA
[3] Department of Pharmacology, Pennsylvania State University College of Medicine, Hershey, PA 17033, USA

With advancing age, the ability of humans to detect and discriminate odors declines. In light of the rapid progress in analyzing molecular and structural correlates of developing and adult olfactory systems, the paucity of information available on the aged olfactory system is startling. A rich literature documents the decline of olfactory acuity in aged humans, but the underlying cellular and molecular mechanisms are largely unknown. Using animal models, preliminary work is beginning to uncover differences between young and aged rodents that may help address the deficits seen in humans, but many questions remain unanswered. Recent studies of odorant receptor (OR) expression, synaptic organization, adult neurogenesis, and the contribution of cortical representation during aging suggest possible underlying mechanisms and new research directions.

Why olfaction and aging?

The decline in the ability to detect and discriminate odors in aged humans leads to a decrease in the quality of life and diminished appetite with accompanying impacts on nutritional status (for a review, see [1]). Decreased olfactory function with aging parallels generalized age-related deficits in sensory functions and cognition that occur in the absence of obvious disease states.

The olfactory system resembles other sensory systems in translating sensory stimuli into distinct perceptions and motivations. However, it is unique in offering an opportunity to use molecular diversity to probe how information extracted from sensory stimuli generates different perceptions. Using this molecular diversity, the field has gained information about the sensory signals generated by different ORs (see Glossary) and begun charting the organization of sensory signals from the nose to the olfactory bulb and hierarchically to the olfactory cortices. These molecular and genetic tools, together with the abundance of information on behavioral responses to odorants, are helpful in dissecting the mechanisms that underlie age-related changes in olfactory function.

Corresponding author: Greer, C.A. (charles.greer@yale.edu).
Keywords: adult neurogenesis; aging; odorant receptor; olfactory cortex; synaptic organization; rostral migratory stream.

0166-2236/$ – see front matter
 http://dx.doi.org/10.1016/j.tins.2013.11.004

The paucity of information available on cellular or molecular changes in the aged olfactory system is startling. A rich and detailed literature documents declines in olfactory acuity, sensitivity, and discrimination in aged human populations, as well as the olfactory deficits that appear with the onset of specific age-related disorders such as Parkinson's disease and Alzheimer's disease (for a review, see [2]). Behavioral studies of olfactory function in aged rodents parallels the findings in humans with decreased sensitivity and ability to discriminate odors (e.g., [3–6]). However, studies of the mechanisms underlying olfaction during nonpathological normal aging are few in number. Rawson and colleagues suggested that isolated human olfactory sensory neurons (OSNs) had a decrease in both sensitivity and selectivity to odorant mixtures, a developmental change that may contribute to age-related declines in olfactory function [7]. However, despite the suggestion that OSN dynamics may change with aging, olfactory bulb glomerular organization of aged humans does not appear

Glossary

Dendrodendritic synapses: synapses occurring between two dendrites. Held in contrast to axodendritic synapses that are polarized from an axonal bouton onto a dendrite.
Glomerulus: spherical neuropil containing the terminal fields of OSNs and the apical dendrites of mitral, tufted, and periglomerular cells. The glomerular neuropil is compartmentalized into regions containing either the axodendritic synapses of OSNs or the local circuit dendrodendritic synapses between mitral/tufted cell dendrites and the periglomerular cell dendrites. Each glomerulus is molecularly specific in that it receives afferent input from OSNs expressing the same OR.
Interneurons: periglomerular and granule cells, the inhibitory neurons of the olfactory bulb both function to inhibit mitral cells via feed-forward and feedback reciprocal dendrodendritic synapses.
Mitral and tufted cells: the primary projection neurons found in the olfactory bulb and receiving synapses from OSNs.
Odorant receptor (OR): a 7-transmembrane G-protein coupled receptor that binds molecular features of odorants with moderate selectivity. Binding of an odorant initiates a signaling cascade that opens cyclic nucleotide-gated channels and an action potential. There are ~1200 different ORs identified thus far in the main olfactory epithelium of mice.
Olfactory cortex: a general term that can include any regions receiving input from the primary projection neurons in the olfactory bulb.
Olfactory sensory neuron (OSN): a bipolar neuron whose apical dendrite arborizes into multiple cilia at the surface of the olfactory epithelium within the lumen of the nasal cavity. The cilia are surrounded by mucous. A thin 0.2 μm unmyelinated axon extends from the basal pole of the OSN and travels as part of the olfactory nerve to the olfactory bulb, without branching until it arborizes within 1 of the ~3700 glomeruli in the olfactory bulb.
Subventricular zone (SVZ): a developmental remnant of the specialized proliferative epithelia surrounding the lateral ventricles. Located on the lateral wall, it is composed of stem cells, intermediate progenitor cells, neuroblasts, and glia. In contrast to most ventricular regions, the SVZ continues to generate new interneurons, periglomerular and granule cells, in the adult. These migrate to the olfactory bulb via an extremely well delineated pathway, the rostral migratory stream.

to differ from younger subjects [8]. Cellular and molecular mechanisms contributing to age-related changes in olfaction are speculative but may include alterations in neuronal populations, synaptic organization, and/or synaptic function. Elsewhere in the central nervous system such changes are proposed to underlie functional deficits (for reviews, see [9,10]). Preliminary work is also beginning to identify candidate genes that may be up- or down-regulated in the olfactory system of aged or injured rodents; work that is likely to provide important clues regarding the mechanisms or events that underlie aging in the olfactory system (e.g., [11,12]). However, for the moment, there are few substantive insights into the cellular and molecular properties of the aged olfactory system, creating a severe handicap in attempting to understand the mechanisms that underlie decreased olfactory function in the elderly. Several reviews appeared in the past few years summarizing the evidence from human olfaction related to aging, senescence, and disease progression, to which we refer the reader [13,14]. In addition, there is a strong interest in the development of mouse models for studying the molecular and cellular substrates of aging-related neurodegenerative diseases such as Alzheimer's [15]. Here, we focus on normal nonpathological aging in rodents and how it may affect the main olfactory system. The authors apologize to those whose work was not included here due to space limitations.

Overview – olfaction and olfactory circuits

As reviewed in Box 1, odors are detected by sensory neurons located in the olfactory epithelium lining the nasal cavity. Once bound to selective ORs, odors elicit a transduction cascade that culminates at synapses with projection and interneurons in the olfactory bulb. Local circuits within the bulb contribute to processing of odor signals

Box 1. Olfactory circuits

Odors are detected by OSNs (1) within the olfactory epithelium lining the nasal cavity (Figure I). Each OSN expresses only one of approximately 1200 different ORs in mice. The odor response profile of a sensory neuron is determined by the receptor expressed. There are 5000–10 000 sensory neurons that express each receptor, leading to a total population of 6–10 $\times$ 10^6 sensory neurons. The life cycle of OSNs is short and they are routinely replaced from a population of basal cells within the epithelium.

Sensory neuron axons coalesce to form the olfactory nerve, which after passing through the cribriform plate distributes over the surface of the olfactory bulb, targeting discrete areas using traditional guidance molecules, cell signaling, and activity [84]. Although the sensory neurons expressing any given receptor can be broadly distributed across the olfactory epithelium, their axons converge on glomeruli (2) based on OR expression. The glomeruli are the site of the first synapse in the olfactory system; the OSN axons form excitatory axodendritic synapses onto secondary projection neurons, mitral (3), and tufted cells (4), and onto a population of interneurons, the periglomerular cells (2). Periglomerular and granule cell (5) interneurons provide feed-forward and feed-back inhibition to the mitral and tufted cells via reciprocal dendrodendritic synapses. Like the OSNs, a process of ongoing adult neurogenesis continuously supplies the olfactory bulb with new interneurons (6) [63].

From the olfactory bulb, the mitral and tufted cell axons target neurons throughout olfactory cortices (7), such as piriform cortex, entorhinal cortex, and the olfactory tubercle, among others. The topographical specificity seen in the coalescence of sensory neuron axons into specific glomeruli is not evident in the cortical projections, which appear broad and diffuse. Beyond these primary olfactory cortices, odor information is passed broadly throughout the neuroaxis to additional cortical and subcortical targets.

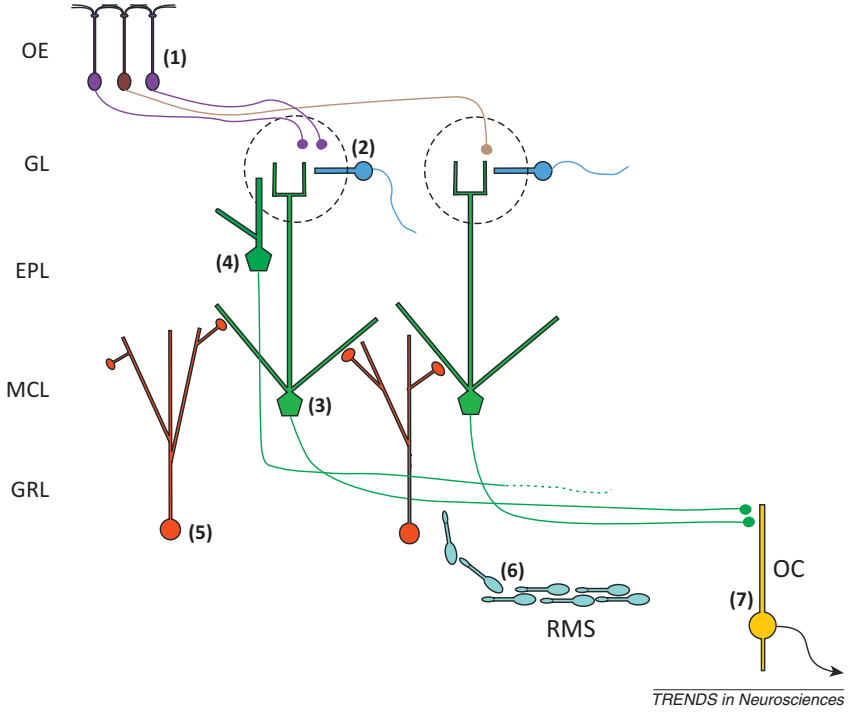

Figure I. Olfactory circuits. Abbreviations: OE, olfactory epithelium; GL, glomerular layer; EPL, external plexiform layer; MCL, mitral cell layer; GRL, granule cell layer; RMS, rostral migratory stream; OC, olfactory cortex.