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Olfaction and Aging: A Mini-Review

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Abstract
Decreased olfactory function is very common in the older population, being present in >50% of individuals aged between 65 and 80 years and in 62–80% of those >80 years of age. Smell dysfunction significantly influences physical well-being, quality of life, nutritional status as well as everyday safety and is associated with increased mortality. Multiple factors contribute to age-related olfactory sensory loss, including nasal engorgement, cumulative damage of the olfactory epithelium from environmental insults, a reduction in mucosal metabolizing enzymes, sensory loss of receptor cells to odorants, and changes in neurotransmitter and neuromodulator systems. In addition, structural and functional abnormalities of the olfactory epithelium, olfactory bulb, central olfactory cortex, and basic olfactory circuitry, which are related to the neuronal expression of aberrant proteins in these areas, may result in olfactory sensory impairment in aging and neurodegenerative diseases. Impaired odour identification is associated with a decrease in cognitive abilities and memory decline. A reduction in the sense of smell is considered to potentially represent an early and important warning of neurodegenerative disorders, particularly of Parkinson's disease and Alzheimer's disease, and, in mild cognitive impairment, olfactory impairment may herald progression to dementia. Further investigations of the potential role of olfactory dysfunction in the early diagnosis and treatment of neurodegenerative diseases are warranted.

Introduction

Olfactory dysfunction is a common feature in the older population, and its prevalence and severity increase substantially with aging; however, relatively little is known about the underlying cellular and molecular mechanisms [1]. Since olfactory dysfunction preferentially associates with a wide range of neurodegenerative diseases, it is regarded as a clinical correlate of Alzheimer's disease (AD), mild cognitive impairment (MCI), Lewy body disease [including Parkinson's disease (PD) and dementia with Lewy bodies], frontotemporal lobar degeneration, and Huntington's disease [2–7]. Disturbances of olfaction are common: 3.8–5.8% of the general population have anosmia (absence of olfaction) [8–10]

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with prevalence rates increasing to 13.9% in individuals >65 years old [11], to over 50% in subjects between 65 and 80 years old, and up to 80% in those >80 years of age, respectively [12, 13]. Since olfactory dysfunction may manifest early in neurodegenerative diseases, it represents an important early clinical symptom suggestive of neurodegeneration [14]. Nevertheless, it also occurs in a large variety of other neurological diseases [2, 12]. Olfactory dysfunction significantly impairs physical well-being, quality of life, enjoyment of food, everyday safety, and is associated with increased mortality in older adults [15, 16]. Multiple (morphological) substrates of olfactory dysfunction have been identified, such as an increased propensity for nasal disease as well as anatomical and functional changes at multiple levels of the olfactory system, including the olfactory epithelium (OE), olfactory bulb (OB), primary olfactory cortices, their secondary targets, and the olfactory circuitry [2, 3, 12, 17]. Impaired odour identification in old age has strong practical implications on daily life activities as it is associated with a decrease in global cognition and a decline in episodic memory [18]. Thus, olfactory functioning may be a valid indicator of the integrity of the aging brain. Unfortunately, the symptomatic relevance and potential (pre)clinical value of olfactory dysfunction remain overlooked by many clinicians [19].

The Olfactory System

Olfactory function plays a critical role in health and behaviour [20]. The olfactory receptor neurons are bipolar cells embryologically derived from both the olfactory placode and the neural crest and form clusters within the respiratory neuroepithelium. They contain 3–50 cilia and send their unmyelinated axons through the cribriform palate to synapses in the OB. Odorants bind to guanidine nucleotide-binding (G) protein-coupled receptors (>500 coding genes but only 100–200 functional receptors) in the cilia of the olfactory receptor neurons. Signal transduction is mediated by activation of the Golf-stimulating adenyl cyclase 3, with 3′,5′-cyclic adenosine monophosphate (cAMP) triggering the opening of calcium-3-activated chloride channels generating depolarization, which is amplified by chloride efflux from the sensory neurons [21]. The number of sensory neurons that serve both as odorant-selective receptor cells and first-order neurons decreases with age, particularly after 65 years of age [22].

Bundles of olfactory receptor axons form the olfactory filia and penetrate multiple foramina of the cribriform plate, which is the thin part of the ethmoid bone that separates the nasal cavity from the brain. Inside the cranial cavity, the glutamatergic receptor cells (periglomerular cells) form the outermost of several layers of the OB that has a hierarchical synaptic organization and is the primary site of processing olfactory information. The modification of these cells occurs by dendrodendritic connections with γ-aminobutyric acid (GABA)ergic granule cells, the activity of which is modulated by centrifugal input from neurons outside the OB, and is influenced by central processes. Axons from olfactory receptor neurons synapse on the dendrites of second-order projection neurons (mitral and tufted cells), forming a special structure called 'glomerulus'. The mitral and tufted cells are the primary efferent projection neurons of the OB. They are excitatory glutamatergic neurons; their dendrite projects to a single glomerulus and receives inputs from the olfactory sensory neurons and lateral dendrites. The incoming axons from the olfactory receptor neurons also synapse on local GABAergic interneurons (periglomerular cells) that are additionally activated by glutamate released from mitral and tufted cells and mediate inhibition within the glomerulus. Glomeruli are the first synaptic relay on the olfactory pathway and play a basic role in smell perception. A second level of olfactory processing occurs at the granular layer of the OB by inhibitory GABAergic neurons that are activated by glutamate released from lateral dendrites of mitral cells, causing inhibition in contrast to enhancement between mitral cells. Like the OE, a number of OB cells undergo periodic replacement as neuroblasts from the subgranular zone (dentate gyrus) and migrate via the rostral migratory stream into the OB, resulting in plasticity within the glomerular region of the OB throughout life [23]. The mitral and tufted cell axons project to central olfactory structures, including the anterior olfactory nucleus (AON), a nodal point in the olfactory system, the olfactory tubercle that is reciprocally connected with the substantia nigra [24], the pyriform cortex (area 51), the largest cortical olfactory area and crucial in odour quality coding, the rostral entorhinal cortex, and the corticobasal nuclei of the amygdala. Since the afferent projections of the olfactory system to the cortex bypass the thalamus, the OB has been suggested to constitute the 'olfactory thalamus' [25]. Subsequent connections are formed with the orbitofrontal cortex (OFC), hippocampus, thalamus, hypothalamus, and cerebellum. All these areas send projections back to the OB, terminating primarily in the granule cell layer. Odour discrimination involves the hippocampus, implicating its role in olfactory working memory [26]. The OFC, a multimodal structure,

plays a vital role in flavour perception, and lesions in this area impair the identification of odours and flavours. The olfactory cortex also receives inputs from cholinergic and monoaminergic neurons in the basal forebrain, hypothalamus, and brainstem [27] Olfactory information is transmitted from the primary olfactory cortex (POC) to other cortical and subcortical areas, all having reciprocal connections with the POC to integrate olfactory information with other sensory modalities [3]. Hence, the olfactory system displays a complex system of centripetal, centrifugal, commissural, and associated connections, as well as reciprocal direct and indirect connections with other essential brain areas [4, 24].

We have recently identified clusters of bipolar neurons expressing the calcium-binding protein secretagogin. These cells are located in an outer 'shell' domain of the olfactory tract and possibly modulate olfactory processing in humans [28].

Age-Related Olfactory Loss in Humans

Assessment of olfactory function is an important part of routine clinical examination [4, 12, 29]. Of note, prevalence rates of olfactory dysfunction obtained by olfaction testing are significantly higher than those merely based on respective patient questionnaires or verbal reports [12].

Age-related deficits in olfactory function are detected by a number of olfactory tests, including psychophysical tests, e.g. odour detection, identification, discrimination, electrophysiological, and psychophysiological tests that generally detect age-related decrements in the olfactory systems [for a review, see 12]. Older people present with heterogeneous olfactory loss, which, however, is more specific to heavier molecules [30].

Causes of Age-Related Loss of Olfaction

Structural changes in the aging nose and olfactory system may explain the functional decline observed in older persons, and a number of age-related alterations within the nose, the OE, the OB, and higher brain structures have been associated with olfactory dysfunction [12]. In addition to changes in non-olfactory elements of the nose (chronic infections, age-related atrophy of the nasal epithelium, a decrease in mucosal blood flow, fluctuations in airflow, imbalance of the sympathetic/parasympathetic mode of olfactory sensibility, reduction in foramina in the cribriform plate, impairment of mucociliar function, etc.), the following changes in the olfactory system ought to be considered: (1) changes in the olfactory neuroepithelium, (2) changes in the OB, and (3) changes in brain regions involved in olfactory processing.

Changes in the Olfactory Neuroepithelium

Age-related changes include a decreased number of receptors, thinning of the epithelium, alterations in olfactory receptor cells, and the replacement of olfactory with respiratory epithelia. The reasons are changes in cell turnover, necrosis of olfactory receptor cells due to an age-related decline in the size and number of the patent foramina in the cribriform plate, impairment of immunologic and enzymatic defence mechanisms critical for maintaining the integrity of the OE, age-related losses in the specificity of the response of individual receptor cells, as well as exposure to air-born environmental agents, including air pollution, cigarette smoke, and xenobiotics. These latter agents as well as genetic factors may determine the degree of olfactory function in later life [31]. Immunohistochemical studies of the OE revealed amyloid-β (Aβ) and paired-helical filament-tau pathology in OE cells and neurofilament-positive dystrophic neurites in neurologically normal elderly persons and in AD patients [32].

Changes in the OB

The size of the OB and the number of its laminae decreases with age in humans and animals, reflecting generalized atrophy, loss of neuronal elements, and increased astroglia, secondary to damage to the OE, as shown in quantitative autopsy studies [33]. Age-related changes in the volume of OB have been documented in vivo using magnetic resonance imaging (MRI) [34], although such decrements are not specific to aging and may occur under several conditions, including smoking, chronic sinusitis, multiple sclerosis, head trauma, and schizophrenia [12]. Correlations were found between odour recognition thresholds and OB volumes in both PD patients ($p < 0.05$) and controls ($p < 0.0001$) [35]. Glomerular degeneration occurs in aged humans with AD, where the glomeruli express Aβ precursor protein, β-secretase, and the γ-secretase complex. The latter has also been shown in transgenic AD models, suggesting that olfactory nerve terminals may undergo age-related dystrophic and degenerative changes associated with increased labelling for amyloidogenic proteins and affecting neurotransmission and integration at the first olfactory synaptic relay [36, 37]. Aβ was shown to disrupt the network activity of the

OB in vitro and can trigger impaired olfaction [38]. While aged controls without MCI performed better on olfactory identification and showed negative Pittsburgh compound B positron emission tomography (PiB PET) amyloid scanning, there were no differences in olfactory identification between MCI cases with or without PiB positivity [39]. In non-demented older persons, neurofibrillary tangles (NFTs) were observed in 35.5–40.5% of OBs, particularly in the AON, rarely in mitral and tufted cells [40]. NFTs are already present in the OB in very early stages of AD and MCI, whereas Aβ plaques have only been described in cases with severe cortical Aβ pathology [41].

Changes in Brain Regions Involved in Olfactory Processing

These changes include a reduction in the volume of the hippocampus, amygdala, piriform cortex, and AON [42]. Age-dependent changes in the number, volume, and localization of islands of Calleja within the olfactory tubercle, a cortical structure receiving monosynaptic input from the OB, may be a contributor to pathological changes in the olfactory cortex function and olfactory perception [43]. Tau and α-synuclein pathology in the OB has been associated with olfactory dysfunction in older non-demented persons, suggesting that here olfactory dysfunction may reflect otherwise 'pre-clinical' neurodegenerative disease, which is neuropathologically characterized by NFTs and Lewy bodies limited to the entorhinal cortex, the CA1 subarea of the hippocampus, and the subiculum [16, 44]. Anosmia per se is correlated with changes within olfaction-related structures, including the piriform and insular cortices, the OFC, the medial prefrontal cortex, the hippocampus, the parahippocampal gyrus, the nucleus accumbens, the subcallosal gyrus, and the medial and dorsolateral prefrontal cortices [45].

Assessment of the Olfactory System

Numerous functional and structural approaches are available for assessing the integrity of the olfaction system. They include psychophysiological, electrophysiological, and imaging tests. Psychophysiological tests of odour sensitivity, identification, and discrimination, notably the University of Pennsylvania Smell Identification Test (UPSIT) and the Sniffin' Stick test, are most widely employed. Most distinct olfactory tests are strongly correlated with one another, although they employ different odorants, have different cognitive demands, and vary in reliability and sensitivity. Threshold studies in larger samples have observed significant threshold deficits in both AD and PD [4]. Variable electrophysiological measures, e.g. odour event-related potentials or an electro-olfactogram to measure smell function, are in use but have received rather little attention in studies of AD and PD, and several other tests are available, e.g. the Self-Administered Computerized Olfactory Testing System (SCOTS) or air-dilution olfactometers [12].

Functional imaging studies, such as functional MRI and PET, demonstrated age-related changes in the processing of olfactory information, e.g. in the inferior and superior frontal and perisylvian regions, the left orbital pole and POC, the amygdala, and the piriform and periamygdaloid cortices [12]; aged adults were showing less brain activity in olfactory structures, consistent with lower ratings of odour intensity [46]. PET imaging of the brain dopamine transporter revealed a significant correlation between olfactory dysfunction and nigrostriatal dopaminergic denervation in the elderly [47, 48]. The ApoEε4 gene may play a role in olfactory functioning that is independent of clinical dementia [49]. In conclusion, olfactory identification and recognition appear the most interesting candidates to be included in a battery to detect subclinical cases of AD, PD, and other disorders [29].

The Olfactory System as a Therapeutic Pathway

The 5-year incidence of olfactory impairment is high in older adults with a history of nasal disorders (polyps, deviated septum) or heavy alcohol use, whereas lipid-lowering agents, regular exercise, and oral steroid use were associated with a decreased risk [50, 51]. The preclinical detection of AD, PD, and other neurodegenerative diseases is critical in determining at-risk individuals in order to improve the planning of the patients' and caregivers' futures and to identify individuals likely to benefit from treatment as advances in therapeutics develop over time [52].

Intranasal delivery of treatment is a feasible option in central nervous system diseases; it may decrease or abolish the side effects seen after systemic administration and can substitute invasive methods of substance delivery. The intranasal delivery of nerve growth factor was found to be effective in animal experiments [53]. The intranasal delivery of insulin has a substantial effect on the synapse function of brain neurons and facilitates memory formation [54, 55, 56]. It avoids hypoglycemia and has no major side effects [57, 58]. In contrast, high-dose vitamin D_2 treatment that regulates the insulin receptor expression

and enhances insulin action was ineffective [59]. It was suggested that non-hydrolyzed carnosine lubricant drug delivery or perfume toilet water formulations combined with related moiety amino acid structures, such as β-alanine, could be explored for their therapeutic potential towards olfactory dysfunction [60]. Hence, further studies are warranted to investigate the potential role of olfactory dysfunction in the life history, prevention, and treatment of age-related nervous diseases.

Conclusion

This mini-review addressed the functional and pathophysiological changes that occur in the human olfactory system as a result of age. Basic information about the anatomy and physiology of this sensory system was provided, along with an overview of the nature and major causes of age-related changes in olfactory perception. Numerous factors are likely to contribute to age-related smell loss, including nasal engorgement, cumulative damage to the OE, changes in the olfactory mucosa, occlusion of the foramina, loss of selectivity of olfactory receptor neurons, changes in neurotransmitter systems, as well as changes in the OB and in the brain regions involved in olfactory processing due to the deposition of pathological proteins associated with various neurodegenerative diseases such as AD and PD. Recent research suggests that there are multiple determinants of olfactory loss in aged persons that may be an early warning of neurodegeneration in the aged brain. Finally, the olfactory system may be a feasible option for the treatment of age-related neurodegenerative disorders.

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