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REVIEW

Aging and chronic inflammation: impacts on olfactory dysfunction-a comprehensive review

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Abstract

Olfactory dysfunction (OD) is a common nasal disease, particularly prevalent among the elderly population, significantly impacting the affected individuals' quality of life. This review focuses on the influence of aging and chronic inflammation on olfactory dysfunction, presenting insights from both the peripheral and central olfactory systems. By exploring the molecular mechanisms and pathological changes underlying the occurrence of olfactory dysfunction in relation to age-related diseases and chronic inflammation conditions, we aim to provide a comprehensive theoretical foundation for further research and offer valuable insights for more effective treatment of olfactory dysfunction.

Keywords Olfactory Dysfunction · Aging · Chronic Inflammation · Olfactory Epithelium · Pathogenesis · Treatment

Introduction

Olfaction is one of the most crucial sensory functions for organisms to perceive the surroundings and protect themselves. It is generated by olfactory sensory neurons (OSNs) in the nasal cavity, which detect volatile chemical molecules. Olfactory dysfunction (OD) refers to a decline in the ability to detect, distinguish, or recall odors [1]. The occurrence of OD may result from various factors such as infection, inflammation, aging, trauma, and idiopathic [1]. Global prevalence studies indicate that OD affects over 20% of the population [2], significantly impacting patients' daily lives and correlating with numerous diseases.

Aging and chronic inflammation are two important causative factors of OD [3], with a mutual influence that further exacerbates olfactory decline. Given the rising aging population in recent years, the impact of OD on the elderly has become increasingly significant. This review aims to summarize the pathogenesis of OD resulting from aging and chronic inflammation, providing theoretical support for related research and treatment strategies.

Aging and olfactory dysfunction

Compared with the young and middle-aged population, the prevalence of OD among the elderly is significantly higher, and increases exponentially after the age of 80 [4]. It has been reported that about 20 ~ 30% of older individuals suffer from diminished olfactory function [5], which is more prominent in disease situation. Dan et al. [3] found that, as age increases, selective loss of odor discrimination is the initial behavioral change in smelling, following by a decrease in odor sensitivity and detection ability, while odor habituation tends to remain intact for a long time. Compared to behavioral changes related to cognitive and motor functions, OD is considered as one of the earliest biomarkers of aging, and also stands as an independent risk factor for mortality [6, 7].

The olfactory system comprises both peripheral (olfactory epithelium, OE) and central components (olfactory bulb and advanced olfactory center). Within the peripheral component, the continuous self-renewal process of basal cells is a fundamental principle for maintaining olfactory function. OD resulting from aging or chronic inflammation is often closely related to changes in the regeneration ability

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of basal cells [8]. OSNs form a synaptic nerve bundle that penetrates the cribriform plate and enters the olfactory bulb (OB) [9]. Figure 1 illustrates the cellular composition and differences of the olfactory system in both young and aged individuals.

Aging in peripheral olfactory system

As age increases, accumulation of various damaging factors and the decline in self-immunity further exacerbate OE damage, leading to a reduction in nasal mucosal blood flow and elasticity, causing a decrease in mucus secretion. These factors contribute to an increased prevalence of nasal congestion, drainage, sneezing, and coughing among the elderly compared to younger individuals [10].

Anatomy studies have shown that OE in elderly animals is typically thinner and often replaced by respiratory epithelium (RE), forming plaques that disrupt the sensory area and block recognition and transmission of odor signals [11, 12]. This anatomical alteration is a econtributing factors to OD.

Under severe injury, OE becomes highly susceptible to respiratory metaplasia. The inhalation of methyl bromide has been regarded as a reliable method for creating an acute injury model of OE. Exposure to methyl bromide in rats results in the sloughing of the majority of the constituent cells of OE, excluding the basal cells [13]. Another model of OE injury involves injection of the herbicide 2,6-dichlorobenzonitrile (DCBN) into mice, leading to the sloughing of OE cells, including some basal cells, resulting in more severe and prolonged injury to OE [14].After methyl bromide-or DCBN induced OE injury, the OE region, which is originally composed of multiple cell layers, is covered by RE consisting only of 1 ~ 2 cell layers. This indicates significant respiratory metaplasia in OE regions [13]. Similarly, significant respiratory metaplasia is observed in the OE of elderly individuals [15], corresponding to the situation after

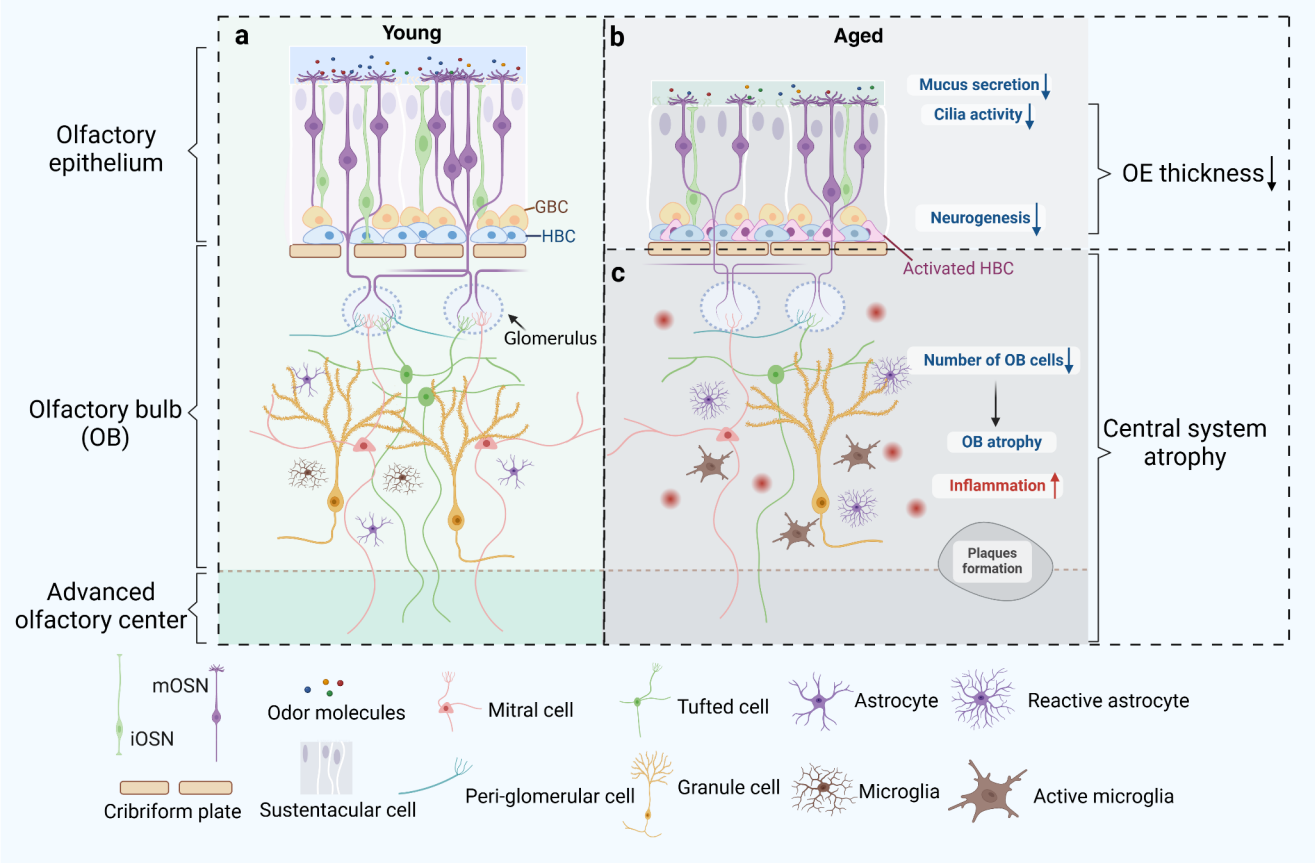

Fig. 1 The cellular composition of olfactory system and changes in young and aged individuals. (**a**) The cellular composition of olfactory system under normal condition (Young). (**b**) Age-related alterations in olfactory epithelium, including OE cells dysregulation, primarily characterized by abnormal activation of HBCs and reduction of mOSNs, as well as decreased mucus secretion and ciliary activity, consequently diminishing the ability to perceive odors. Meanwhile, the mucosal layer undergoes thinning and the number and size of the cribriform foramina reduce with advancing age, leading to a decline in the transmission of odor signals, thereby impairing the olfactory function. (**c**) Age-related alterations in olfactory bulb primarily include the reduction of the number of OB cells, resulting in OB atrophy. As inflammation intensifies, glial cells become abnormally activated. Furthermore, the plaques formed in the central olfactory system increases with advancing age. mOSN: mature olfactory sensory neuron; iOSN: immature olfactory neuron; HBC: horizontal basal cell; GBC: globose basal cell

DCBN injury [14], with the majority of newly generated ciliated cells originating from HBCs. The aging process also leads to structural changes in OE, characterized by a reduction in the number and size of the cribriform foramina. Consequently, the axons of OSNs that extend from OE to the central nervous system become compressed or even disappear, resulting in a decline in the efficiency of olfactory information transmission [10, 16]. Additionally, volatile stimuli require dissolution and penetration of mucus to bind to the olfactory receptors (ORs) located on the corresponding neuronal cilia. As age increases, the secretion and hydration function of mucus decrease, leading to reduced ciliary activity and prolonged retention of stimulating chemicals on neuronal cilia, which exacerbates damage to OE [17]. Figure 1b depicts the aging-related changes in peripheral olfactory system, especially in OE.

The most prominent manifestation in the nasal cavity is dysregulation of OE cells' regeneration [18]. The basal cells in OE can be divided into horizontal basal cells (HBCs) and globose basal cells (GBCs). Under normal conditions, HBCs are typically quiescent stem cells; whereas GBCs can generate both OSNs and non-neural cells, such as sustentacular cells (SUS) and Bowman's duct/ gland cells [19, 20]. The differentiation of GBCs and normal function of HBCs are important factors in neurogenesis [13, 14]. When OE is injured, the plasticity of progenitor cells alters, causing HBCs to become activated and differentiate rapidly into GBCs, leading to the development of immature OSNs (iOSNs) into mature OSNs (mOSNs) [21]. Meanwhile, activated HBCs can also differentiate into non-neural cells, and even respiratory epithelial cells, which may explain the respiratory metaplasia observed in OE after injury [22, 23].

Following OE damage induced by methimazole, notable activation and proliferation of HBCs were observed on the third day, with this phenomenon rapidly recovered to baseline levels by the fifth day [22]. However, this regeneration ability is not infinite. In aged OE, there is an increase in OSNs death and a decline in the activation of GBCs. HBCs appear to have a greater tendency to enter the cell cycle rather than differentiating into SUS or neuronal cells, and they exhibit a more robust interaction with immune cells [18]. It was once widely believed that aging may lead to a decrease in the number of GBCs and mOSNs in OE, while HBCs still persist in the quiescent phase [15]. However, Li et al. found that there is a separate group of activated HBCs in the OE of elderly mice, which highly express Krt6a and Krtdap, but this group does not participate in the renewal of SUS and OSNs, and instead has stronger interactions with neutrophils. Therefore, the role of this group of activated HBCs still needs further exploration [18].

Multiple signaling pathways, including Notch and Wnt pathways [24], are integral in the regeneration of HBCs. For instance, leucine-rich repeat-containing G-protein-coupled receptor 5 (Lgr5) is a molecule of the Wnt signaling pathway that plays an important role in embryonic development and adult tissue regeneration. It exhibits dynamic expression during the repair of injured tissue. When OE is damaged, $Lgr5^{+}$ cells are recruited and function as multipotent stem cells, which can be either GBCs or HBCs, playing a significant role in regenerating OSNs and SUS during epithelial repair process [24, 25].

The transcription factor p63 is essential for maintaining the dormancy of HBCs in OE [26]. Herrick et al. found that, contrary to the situation in most tissues, enhanced Notch activity can elevate the expression of p63. Following the inhalation of methyl bromide, the Notch signaling diminishes in OE, thereby prompting the repair process after OE damage [27]. Notch signaling promotes the differentiation of non-neuronal cells, whereas blocking classical Notch signaling significantly increases the proportion of neuronal differentiation [23]. Activation of Notch signaling leads to more cells in OE being maintained in a progenitor or immature state, resulting in the production of more proliferating progenitor/stem cells, but fewer mature neuronal cells. In addition, inhibiting Notch can enhance the generation of mature sensory neurons in olfactory organoids and reduces the number of proliferating cells [28]. Interestingly, it has been reported that Notch is activated in the elderly OE [29], which may further confirm the inhibitory effect of aging on the activation and differentiation of HBCs.

Olfactory receptors (ORs), expressed in mOSNs andresponsible for transmitting odor signals to the central nervous system, belong to the family of G protein coupled receptors (GPCRs). Signal transduction in ORs depends on the combination of a GTP binding protein, which subsequently activates type III adenylate cyclase, catalyzing the formation of cyclic adenosine monophosphate (cAMP) [10, 30]. cAMP in nasal mucus plays a pivotal role in stimulating the growth and maturation of olfactory stem cells and inhibiting apoptosis. Studies have shown patients with OD exhibit significantly lower cAMP levels in nasal mucus, compared to healthy individuals. Furthermore, it has been observed that the cAMP levels decrease with age after 50, aligning with the age-related changes in OD. However, after reaching 70 years of age, cAMP levels exhibit an upward trend, suggesting a potential functional compensation mechanism for residual ORs [31–33]. To date, there have been few reports on the impact of aging on ORs, and further research in this area is needed.

Aging in central olfactory system

The olfactory bulb (OB) is organized into six layers, ranging from superficial to deep: olfactory nerve layer (ONL),

glomeruli layer (GL), external plexiform layer (EPL), mitral cell layer (MCL), inner plexiform layer (IPL) and granule cell layer (GCL). These layers collectively facilitate the OB's diffuse projections to higher cortical regions, which regulate olfactory behavior [34]. The morphology of OB undergoes alterations with age [35]. The ONL of OB is prominently thinner in adults, and the GL tends to be more irregularly arranged [12]. MRI studies show that, in individuals with normal olfactory function, OB typically resembles the shape of an olive. Conversely, patients with OD often exhibit abnormal OB shapes, such as convex, concave, or irregular forms [35]. Moreover, significant OB atrophy has been observed in elderly individuals, which may be attributed to a reduction in the number of OB cells, particularly glomerular cells and mitral cells [10, 36]. These changes collectively contribute to age-related impairment of olfactory function.

Furthermore, research on elderly OD patients have unveiled various metabolite alterations in OB associated with aging [3], leading to impaired function of OSNs and other OB cells. One notable finding is the significant decrease in nicotinamide adenine dinucleotide (NAD^+), an important component of redox reactions, with age. Supplementation with NAD^+ has been shown to extend the lifespan of aged mice while restoring their sense of smell [3]. Another significant change is the sharp decline in abundance of glycerol, which affects cell morphology and function in multiple ways and impairs OSNs function. Moreover, the cholesterol level gradually increases with age [37]. Cholesterol plays a significant role in maintaining glial cell function, however, excessive activation of glial cells in elderly OB can exacerbate inflammation and cause OD. Figure 1c illustrates the changes in OB among the elderly population.

During aging, significant atrophy and plaque formation occur in olfactory related regions of the central nervous system, such as piriform cortex, anterior olfactory nucleus, and hippocampus. These changes contribute to the progression of OD in the elderly [38]. Throughout the aging process, both morphology and function of the primary olfactory cortex undergo changes. These lesions are also commonin patients with neurodegenerative diseases. Consequently, researches of alterations in higher olfactory center are closely related to neurodegenerative diseases, as will be elucidated in the following section.

Olfactory dysfunction and neurodegenerative diseases

The aging process leads to the pathological aggregation of proteins, impairs early synaptic plasticity, and selectively disrupts neural networks. This results in oxidative damage and neuroinflammation in brain, ultimately causing plaques formation in multiple structures of the central nervous system, including the olfactory center [39, 40]. Several studies have established robust correlations between OD and neurodegenerative diseases such as mild cognitive impairment (MCI), Alzheimer's disease (AD), and Parkinson's disease (PD) [41, 42]. Moreover, OD has been confirmed as an early indicator of age-related neurodegenerative diseases, often occurring prior to the manifestation of cognitive and motor dysfunction [43].

Alzheimer's disease (AD), a persistent and destructive disease that gradually impairs memory, thinking and action abilities, has a high incidence rate among the elderly, affecting about 10.9% in individuals over 65 years old [44]. OD can occur in the early stages of the disease, particularly with a significant decline in olfactory recognition ability, and the severity of olfactory damage increases as the disease progresses [45]. The biomarkers of AD include β amyloid deposition, pathological precipitation of tau protein, and neurodegeneration. In addition, atrophy of related brain regions, such as hippocampus, is often used as one of the diagnostic factors for AD [46]. Notably, these pathological changes are also observed in OD patients, with a significant reduction in gray matter and hippocampal volume visible on MRI. These phenomena occur in the olfactory system prior to the onset of cognitive impairment, which hindered the processing of odor signals by the olfactory center and exacerbated the degree of OD [38, 47]. A study on dementia patients indicated that greater brain atrophy dominated by the amygdala (also proved to be related to olfactory recognition and cognitive ability), is associated with severe declines of olfactory function [48]. APOE ε4 allele is a major genetic risk factor for AD, which also exists in the olfactory system and is positively correlated with the occurrence and severity of OD [49]. Studies have revealed that individuals harboring the APOE ε4 allele, when accompanied by OD, exhibit a markedly elevated risk of developing dementia [50].

Another common neurodegenerative disease is Parkinson's disease (PD). The main clinical manifestations of PD include bradykinesia, static tremor, and gait stiffness. The pathological changes of PD include abnormal loss of dopaminergic neurons in the substantia nigra and other related brain regions, formation of Lewy bodies, as well as misfolding and aggregation of α-synuclein, the main component of Lewy bodies [51]. Studies have reported that these PD-related pathological changes also occur in the OB of OD patients. As the progressing of PD, these lesions gradually spread to the higher olfactory center [43].

Furthermore, age-associated nigrostriatal denervation (AASDD) frequently manifests during the natural aging process, with a more pronounced occurrence in elderly individuals. According to reports, there was a strong association between OD and AASDD among the elderly population [52,

53]. The dopaminergic system, which plays a crucial role in neural aging, is also related to olfactory function. Studies conducted on healthy, dementia-free elderly subjects have shown that OD is associated with dopamine denervation and the reduced binding of dopamine transporter [52, 54].

These findings strongly indicated a close correlation between OD and the neurodegenerative diseases. Hence, early diagnosis of OD may enable timely intervention to prevent or slow down the progression of related diseases [55].

Chronic inflammation and olfactory dysfunction

Among the various factors contributing to olfactory dysfunction, the sinus/nasal diseases characterized by chronic inflammatory conditions, account for a significant proportion (29.97∼78.23%), trailing only behind viral infection [56]. As a representative chronic inflammatory disease, chronic rhinosinusitis (CRS) has a high incidence yet lacks effective treatment modalities. It is estimated that about 60∼80% of CRS patients suffer from OD, with an even higher incidence observed in those with nasal polyps. This OD often persists a long-term and, in some cases, may lead to complete loss of olfactory function, significantly impacting patients' quality of life [57]. Damage to the olfactory system and inflammatory infiltration have also been identified in a mouse model of eosinophilic chronic sinusitis [58].

Chronic inflammation in peripheral olfactory system

Inflammation is a process involving the recruitment of immune cells and secretion of pro-inflammatory factors. Immune cells, such as macrophages, T lymphocytes, and dendritic cells, can secrete growth factors and cytokines to activate the downstream stem cell pathways, thereby improving body's self-renewal and resistance. Wnt, Notch and NF-κB, are classic stem cell signaling pathways involved in this process [59]. Therefore, the regulation of immune system directly affects the regenerative capacity of stem cells, promoting tissue repair and regeneration [59, 60]. The regeneration of OSNs after injury depends on the proliferation and differentiation of stem cells, which means repair process of OE after injury is a self-limited inflammatory response of the local immune system [21, 25].

In the early stages of OE injury, immune cells such as macrophages and T cells migrate to the injured area to clear damaged cells and pathogens. These cells release cytokines, which regulate the inflammatory response and initiate the regeneration of HBCs. TNF-α is a primary cytokine participates in inflammatory response. Research has found that after acute injury, inflammation is suppressed and the proliferation ability of HBCs is weakened in TNF-α receptors knockout mice. Therefore, anti-inflammation treatment at this stage inhibits the regeneration of OSNs [61]. However, with further infiltration of immune cells and increased production of pro-inflammatory mediators, chronic or excessive inflammation can lead to changes in the structure and function of olfactory system, thus neuroepithelial stem cells undergo functional transition from regeneration to immune defense, restrain the maturation of OSNs [62]. For instance, Bowman's glands produce a special layer of mucus that covers the olfactory neuroepithelium, composed of odorant binding proteins and specific ions that promote the transmission of olfactory signals. Chronic inflammation in OE disrupts its barrier function, weakens ciliary function, damages the microenvironment, and blocks the transmission of olfactory signals [63]. The levels of inflammatory factors such as IL-6, IL-5, IL-13 in the nasal cavity is inversely proportional to the olfactory function of the subjects [64]. On the OE tissue biopsy of CRS patients, it was found that the original pseudostratified epithelial cells were gradually replaced by squamous-like cells, indicating severe squamous metaplasia occurs in OE patients with CRS. Meanwhile, loss of SUS and mature neurons was observed in the original OE location, which means OE was replaced by RE [65].

CRS is categorized into type 2 and non-type 2, with polyp-associated type (CRSwNP) predominantly belonging to type 2 [66]. The physical obstruction caused by nasal polyps in the olfactory cleft is the most intuitive factor affecting olfactory function. Experimental studies have shown that after odor deprivation treatment [67], the OB and anterior olfactory nucleus of mice contract. The atrophy of OB after long-term odor deprivation may be due to the reduction of newly generated neurons caused by weakened odor enrichment [67]. In addition to mechanical obstruction, increased tissue inflammatory factors and the release of cytotoxic substances can also cause local destructive effects. Patients with CRS experience epithelial remodeling and the formation of nasal polyp, but their nasal immune barrier is also damaged due to the abnormal accumulation of leukocytes and other inflammatory factors [68]. This explains why anti-inflammatory treatment is effective to release the symptom of OD [64]. A large amount of eosinophil infiltration was found in OE of CRSwNP patients with OD, and eosinophil proliferation is also a characteristic feature of CRSwNP [69]. The massive infiltration of eosinophil in the olfactory mucosa may disrupt the integrity of OE, thereby affecting the regeneration of OSNs and leading to sustained OD [65]. Meanwhile, non-type 2 CRS, represented by CRS without polyp (CRSsNP), performance the type 1 immune response mediated by THF and IFN will transform basal cells from nerve regeneration to immune defense [62].

Chronic inflammation in central olfactory system

Chronic inflammation within the nasal cavity also triggers neuroinflammation in OB, inducing activation of glial cells and increase in inflammatory factors such as IL-1β and TNF-α. Neuroinflammation in OB results in the reduced activity of OSNs and decreased number of OB cells, which is the primary cause of OB atrophy [67]. Previous studies further revealed that OB that had undergone atrophy did not fully recover to normal level for a considerable period after cessation of pro-inflammatory stimulation. While neuroinflammation in the CNS may have a protective effect on neurons, chronic neuroinflammation often has more destructive impacts than protective functions, resulting in significant damage [70]. Intranasal administration of lipopolysaccharide (LPS) can induce chronic inflammation with activated glial cells and synaptic loss in OB [71]. Prolonged inflammation for 10 weeks or longer can lead to OB atrophy, predominantly affecting the superficial layers of OB, including the ONL, GL, and EPL, with EPL being particularly affected. The atrophy of ONL and GL is attributed to the loss of OSNs axons and the damage to OE caused by persistent nasal inflammation. The atrophy of EPL is linked to the activation of glial cells and increased production of pro-inflammatory factors [72, 73].

Long-term inflammatory infiltration of the OE can be transmitted to the central olfactory system through the olfactory sheath, gradually transmitted to the brain through intercellular interactions, causing local encephalitis and probably hindering the reception of olfactory signals [71, 74, 75]. Glial cells are crucial for maintaining neuronal homeostasis, especially astrocytes and microglia [76]. When the CNS is damaged by inflammation, astrocytes undergo abnormal reactivity, inducing activation of microglia. These microglia secrete factors such as IL-1β and TNF, further inducing the reactivation of astrocytes. Reactive astrocytes lose their ability to promote neuronal survival, synaptogenesis and phagocytosis, causing the occurrence of diseases related to neuro-regeneration [61, 75]. Research on elderly subjects often exhibits a large number of abnormally activated glial cells in brain tissue, reflecting damage to OSNs and OB neurons, which significantly affects olfactory function in the elderly [76, 77]. Figure 2 illustrates the damaging effects of inflammation.

Long COVID-19 related olfactory dysfunction

Viral infection, represented by COVID-19, constitutes one of the most prevalent causes of OD, often initiating with acute inflammation. In the majority of cases, viral- induced OD is self-limited and resolves within two weeks. However, in rare cases, a small proportion of patients (10 ~ 17%) may experience permanent OD or even complete loss of smell following recovery from COVID-19 [78]. Individuals with COVID-19 related OD exhibit elevated levels of inflammatory factors such as INF-γ and IL-6 within the olfactory system. Subsequently, during the post-acute infection phase, the excess inflammatory factors are not completely eliminated and infiltrate adjacent tissues, transitioning towards chronic inflammation, which emerges as a critical factor contributing to refractory OD [79]. Furthermore, patients with OD resulting from COVID-19 exhibit an increased probability of new diagnoses of AD, with associated brain regions also being affected [7].

The underlying pathogenesis of consistent OD due to post-viral olfactory dysfunction (PVOD) remains elusive. Direct damage inflicted by viruses on the SUS of OE is also among the significant contributors to the development of OD. Nevertheless, it is undeniable that chronic inflammation plays a crucial role in the onset and progression of OD [80].

Aging and chronic inflammation

Chronic inflammation is a mechanism of aging and can promote the aging process, with the levels of inflammatory markers being closely related to the degree of aging [81].

Interactions between aging and chronic inflammation

Chronic inflammation is an essential part of the hallmark of aging [82]. As individuals age, there is a general increase in inflammation throughout the body, both locally and systemically. This reflect in the higher incidence of inflammatory diseases such as arteriosclerosis, osteoarthritis, intervertebral disc degeneration, among others [83]. Meanwhile, the elevated levels of inflammatory cytokines and biomarkers in the elderly population contribute significantly to the prediction and prevention of geriatric medical conditions, which are associated with increased risk and mortality [81, 83]. Chronic inflammation is a complex outcome of multiple changes in the body due to aging, including genomic instability, telomere shortening, mitochondrial dysfunction, epigenetic alternation, cellular senescence, and stem cell exhaustion. While being a consequence of these alterations, chronic inflammation also accelerates the aging process. Conversely, interventions targeting chronic inflammation have the potential to delay aging and potentially treat aging-related diseases [82].

During aging, cells are exposed to a variety of oxidative stressors and irreversibly cease mitotic activity. Some cells undergo apoptosis, while the surviving ones release

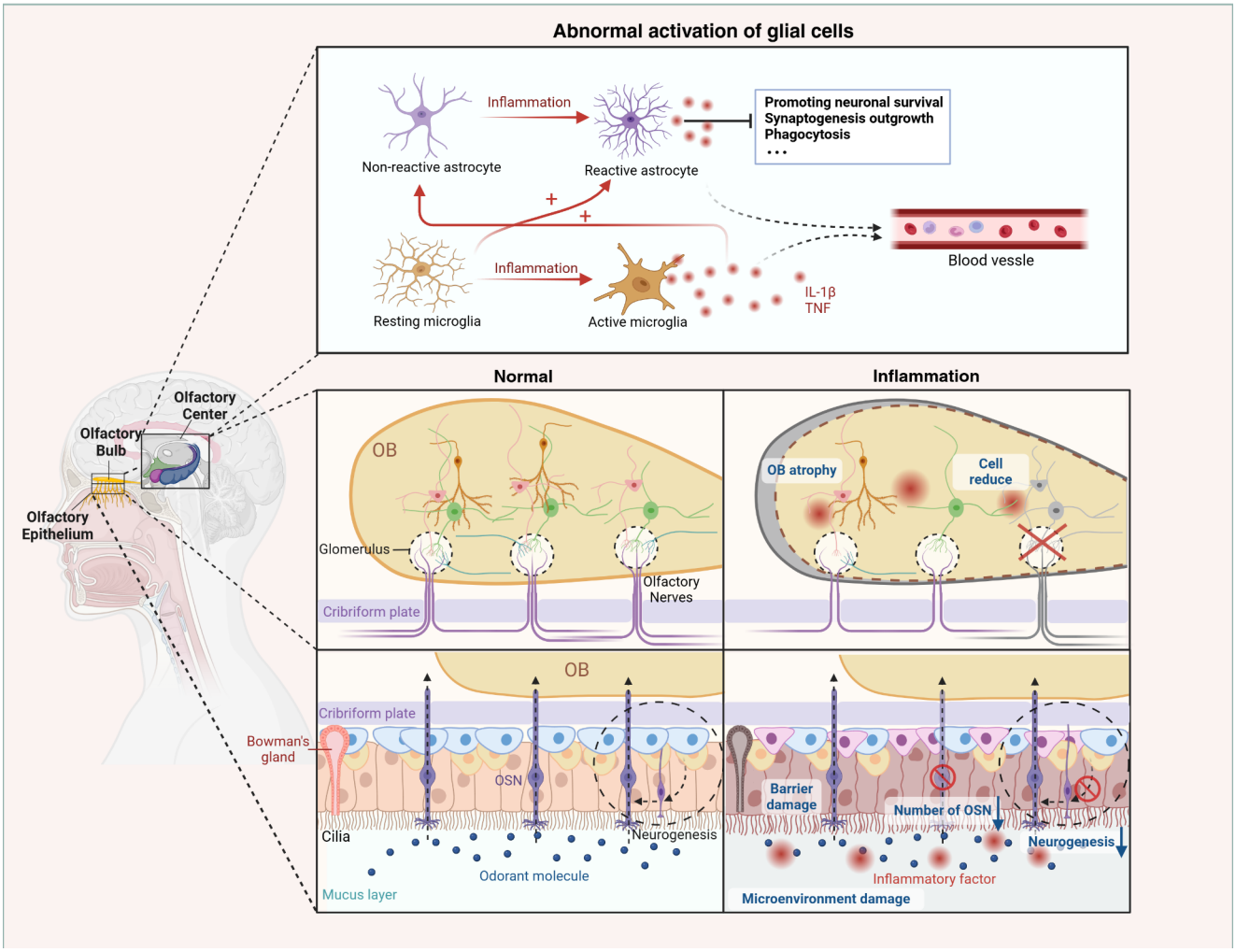

Fig. 2 The detrimental effects of inflammation on the olfactory system. Chronic inflammation in OE alters the microenvironment, breaking the barrier function of olfactory epithelium, thinning the mucus layer, reducing the number of OSNs, and impeding the transmission of odor signals. Infiltration of inflammatory factors also reduce the number of OB cells, contributing to OB atrophy. Meanwhile, long-term rhinitis inflammation affects CNS, triggered abnormal activation of glial cells, especially astrocytes and microglial which release additional inflammation factors such as IL-1β and TNF throughout the body. Collectively, these effects collectively promote the damage to the sense of olfaction

inflammatory cytokines, such as IL-6 and TNF-α. This phenomenon is known as the senescence associated secretory phenotype (SASP). Simultaneously, once cells enter a senescent state, intracellular chromatin undergoes reorganization, leading to widespread changes in gene expression and increased inflammation within the body [84]. The accumulation of reactive oxygen species (ROS) in aging cells not only accelerates the aging process of cells and organisms through a feedback effect, but also leads to multiple organ dysfunction and the formation of chronic inflammation in the body [84, 85]. Glial cells activation, particularly astrocytes and microglia in the central nervous system (CNS), has been found to be positively correlated with inflammation. These cells significantly activated in the elderly, exhibit abnormal functions, indicating a heightened inflammatory reaction in the aging brain [76, 86, 87].

Aging and chronic inflammation exacerbating impact on olfactory dysfunction

Although inflammation is necessary for the body's defense against external damage and eliminating harmful substances, it often manifests as immune imbalance and overactivation in the elderly, thereby promoting disease progression [88]. In elderly individuals, a significant infiltration of inflammatory cells can be observed on OE [15, 18]. A study on atherosclerosis and olfactory function in the aged population has indicated a positive correlation between the two conditions. The presence of plaques correlates with the risk of

OD. Early atherosclerosis may serve as a risk factor for age-related olfactory impairment, or even accelerate aging process. This correlation is strongly associated with increased levels of inflammatory factors in the patient's plasma [89]. Inflammatory changes in the stem cells of OE may lead to age-related OD by disrupting normal epithelial homeostasis, resulting in the replacement of the original neuroepithelium of OE with squamous epithelium [90]. In other words, even there is no lesion outside, certain regions of OE may still be replaced by RE [91]. According to reports, the inflammatory response phenotype observed in HBCs of aged rats aligns with aging-related tissue changes. This inflammatory response can trigger autoimmune defense response in OE, inhibiting normal neurogenesis and potentially exerting a neuroprotective role. This phenomenon may also be related to the loss of OSNs and hinder basal cells proliferation [62, 90, 92].

As the years pass, the inflammatory response in brain regions associated with olfactory function. Studies have observed significantly elevated levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, in the plasma of elderly mice [3]. TNF-α has been proven to affect the function of OSNs and neuroepithelial regeneration, with its overexpression being extremely important for the pathogenesis of OD [93]. In elderly individuals, changes in glial cells become more remarkable, significantly exacerbating damage to the advanced olfactory center and accelerating the procession of OD [86]. Furthermore, chronic inflammation has also identified as a mediator of pathological declines in cognitive function in both human and animal studies [81]. Figure 3 summarizes the common characteristics shared between aging and chronic inflammation, and how their interaction further leads to the progression of OD.

Clinically significant and therapeutic perspectives

Clinical diagnosis and assessment

Many patients experience adverse consequences of olfactory dysfunction without recognizing the condition, emphasizing the crucial role of early diagnosis in treating and managing OD [94]. Various methods have been reported for assessing OD, including psychophysical, electrophysiological and psychophysiological tests. Currently, the University of Pennsylvania Smell Identification Test (UPSIT) and Sniffin's Sticks from Germany are the most common testing methods.

Potential therapeutic strategies

While most cases of OD are self-limiting, especially those caused by viral infection, there are still quite a few cases that require treatment. The treatment of OD mainly involves preventing and treating the primary disease, preventing or slowing down the progression of OD, and improving the existing olfactory symptoms.

Among the existing drugs, glucocorticoids are the most commonly used. Long-term local corticosteroid administration and short-course systemic steroid administration when symptoms worsen are currently the standard methods for treating OD, especially in cases caused by CRSwNP [95]. Others, such as estrogen, biological agent, IGF-1, theophylline, vitamin A and sodium citrate are also being attempted for clinical use [96–101]. Additionally, traditional Chinese acupuncture (TCA) and surgery are used in adjuvant therapy of OD [102, 103]. Among all treatments, olfactory training (OT) is confirmed to be the safest and most feasible method for treating OD, and it has been widely used during the COVID-19 pandemic [104, 105]. OT was initially proposed by Hummel et al. in 2009 [106], the specific method involves exposing patients to four selected odorants (phenyl ethyl alcohol, eucalyptol, citronellal, and eugenol) twice a day for a duration of 12 weeks, followed by periodic assessments of the patients' olfactory function. OT has been found to play an important role in promoting the regeneration of OE and OB, as well as maintaining the maturity of the olfactory center. In elderly individuals, after a period of OT, there is a significant improvement in the decline of smell, memory, and cognitive function caused by aging or neurodegenerative diseases, which increases the subjective well-being of subjects. This effect has been found to be related to structural changes in the olfactory related areas of the brain [107, 108]. After 4 months of OT on MCI patients, an increase in the volume of the olfactory cortex and the thickness of the bilateral hippocampal cortex were observed. These phenomena reflect that continuous OT not only improves patients' olfactory function, but also delays the occurrence and progression of neurodegenerative diseases in the elderly, making it a highly valuable treatment option [109].

Conclusion

This review summarizes the existing reasons for the significant increase in the prevalence of OD among the research findings. However, current research has yet to fully elucidate the mechanisms underlying the impact of aging and chronic inflammation on OD. Additionally, the majority of existing research is confined to OE and OB, with a notable

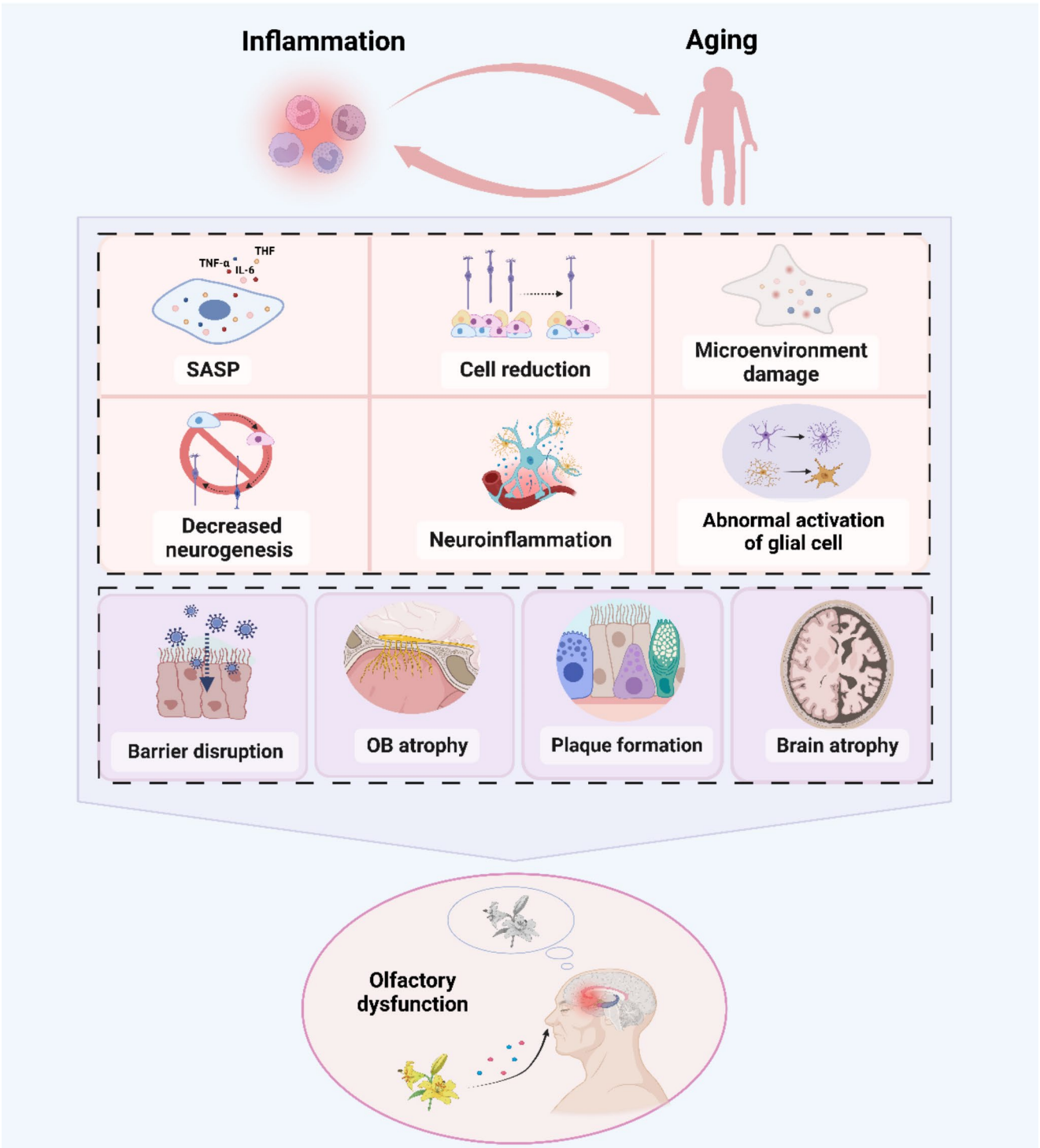

Fig. 3 Pathogenesis of olfactory dysfunction on aging and chronic inflammation (molecular and anatomical changes). As two important pathogenic factors, aging and chronic inflammation can exhibit SASP, promote the secretion of inflammatory factors, cause the reduction in number and function of cells related to odor reception and transmission, damage the microenvironment of olfactory mucosa, decrease neurogenesis, intensify local and overall neuroinflammation, causing abnormal activation of neuroglial cells especially astrocyte and microglia in advanced neural center. Moreover, aging and chronic inflammation mutually interact and potentiate their effects through a series of complex mechanisms. These molecular level changes further cause anatomical structural alterations, such as barrier disruption, plaque formation, OB and brain parenchyma atrophy. These alterations in turn exacerbate the processes of aging and chronic inflammation, ultimately leading to OD

lack of understanding of the mechanism governing higher level of olfactory centers. Meanwhile, research on the peripheral olfactory system and primary olfactory centers is far from conclusive. Consequently, it is urgent to explore the mechanism underlying lesions in the central olfactory system. Nowadays, the pressure of daily life has reached unprecedented level, with insomnia and circadian disruption becoming common occurrence. These issues may be related to OD, leading to a higher number of people suffering from OD in the future. Additionally, these issues are prevalent among the elderly [110]. Due to the lack of awareness regarding hazardous gases and the presence of potential mental diseases, coupled with the absence of nearby individuals to provide warning signals, OD poses a significant risk to elderly living alone. Longevity has gained significant global attention, leading to increased focus on health management and enhancing the quality of life for the elderly. Therefore, it is imperative for researchers to delve deeper into aging-related changes, further refine the understanding of OD pathogenesis, and develop more effective drugs or technologies to address this issue.

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Declarations

Consent for publication All authors agree to publish this review.

Conflict of interest The authors have declared that no competing interest exists.

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