

Olfactory dysfunction and COVID-19



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Here, we provide an overview of olfactory dysfunction associated with COVID-19. We provide background regarding the organization and function of the peripheral olfactory system. A review of the relevant literature on anosmia and parosmia due to infection with SARS-CoV-2, the virus causing COVID-19, is provided. Specific attention is focused on possible mechanisms by which the virus may interact with and damage the cell populations of peripheral olfactory system. Evidence from human studies as well as animal models is considered. Finally, we discuss current recommendations for evaluation and management of patients with persistent post-COVID olfactory dysfunction, as well as possible future research directions.

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Introduction

Olfaction involves the detection of volatile odor molecules at a peripheral sensory epithelium in the nose, delivering input via the first cranial nerve to the olfactory bulbs of the brain. The bipolar olfactory sensory neurons, lining the olfactory cleft superiorly in the nasal cavity, are activated by odors binding to G-protein coupled olfactory receptors, and their axons synapse in the glomerular layer of the olfactory bulb.¹ A functional olfactory system permits the detection of a vast arrays of odors,² and also contributes to the perception of flavors in combination with gustatory input from the taste buds, alerts us to environmental dangers, influences social interactions, evokes emo-

tional states, and supports learning and memory.^{3,4} The inability to perceive odors, therefore, can significantly affect nutritional intake, avoidance of harmful fumes and spoiled foods, and can lead to social isolation, depression, cognitive decline, and even increased mortality.^{5,6} Prior to the COVID-19 pandemic, an estimated 13.3 million people in the United States (aged ≥ 40 years of age) were affected by some form of olfactory dysfunction, with increasing prevalence of olfactory loss among older age groups.⁷

The demographics of humans suffering with olfactory dysfunction has changed dramatically since the onset of the current COVID-19 pandemic.⁸ In late 2019, an outbreak of a novel coronavirus infection starting in Wuhan, China led to the COVID-19 pandemic, causing infections ranging from mild or asymptomatic disease to pneumonia, severe illness, and death.⁹ We now know that chemosensory dysfunction is a hallmark of COVID-19 and can be present regardless of the severity of illness.¹⁰ In 2 cross-sectional studies, recent chemosensory dysfunction was identified

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as a predictor of having COVID-19.^{11,12} A majority of patients with COVID-19-associated loss of smell recover function within a few weeks.¹³ However, persistent olfactory dysfunction was identified as one of the symptoms among patients with Post-Acute Sequelae of SARS-CoV-2 infection (PASC).^{14,15} Recent evidence suggests that up to 7% of subjects may remain anosmic >12 months after onset, with higher percentages suffering from hyposmia or parosmia.¹⁶ Even higher percentages of PASC subjects report suffering from hyposmia, parosmia, and phantosmia,^{10,17} which may last a year or longer. Here, we discuss the possible mechanisms underlying olfactory dysfunction in patients infected by SARS-CoV-2, the clinical evaluation of olfactory dysfunction, current treatment options, long-term impacts of olfactory dysfunction in the setting of the ongoing COVID-19 pandemic, and future research.

Mechanisms

A number of viruses causing upper respiratory infections in humans, including coronaviruses or influenza, can cause transient or permanent olfactory loss.¹⁸⁻²⁰ However, SARS-CoV-2 can cause a rapid onset anosmia even in the absence of other severe symptoms, suggesting it may interact with olfactory cell populations in unique ways. Thus, understanding how the virus enters human epithelial cells, and which cell types within the peripheral olfactory system are viral targets, were key early questions.

While several cell surface receptors and protease cofactors are known to mediate cellular entry for coronaviruses related to SARS-CoV-2, it has been established that the surface receptor ACE2 interacts with the SARS-CoV-2 spike protein, mediating viral entry, and that the enzyme transmembrane protease serine 2 (TMPRSS2) functions as a co-factor.⁹

As a key step towards understanding how SARS-CoV-2 interacts with the peripheral olfactory system, the sustentacular cells of the olfactory epithelium were identified as likely viral targets.²¹ These studies, involving the analysis of single cell RNA-sequencing datasets from human olfactory mucosa, human respiratory mucosa, and murine olfactory mucosa and olfactory bulb, found that sustentacular cells co-express the necessary viral entry genes ACE2 and TMPRSS2. Additional studies reanalyzing data²² or performing immunohistochemistry²³ confirmed these findings. In agreement, a hamster model of SARS-CoV-2 infection found that viral particles indeed localized to olfactory epithelium sustentacular cells, rather than olfactory neurons.²⁴ Moreover, human autopsy histology studies performed on subjects who died from severe COVID-19 also identified virus specifically in olfactory sustentacular cells.²⁵ That sustentacular cells, not neurons, are infected by the coronavirus was perhaps surprising, given the rapid and complete anosmia occurring with COVID-19, and has raised additional questions regarding olfactory mucosal function and homeostasis.

Olfactory mucosa

What are the sustentacular cells of the olfactory epithelium, and what is their normal function? Lining the olfactory cleft along the superior posterior nasal septum and medial vertical lamellae of the superior turbinates, the olfactory epithelium contains several distinct cell populations (Fig. 1A). The middle layers of the epithelium contain the somata of the primary olfactory sensory neurons, whose dendrites extend to the apical surface of the epithelium. Emerging from the dendritic knob are several immotile neuronal cilia. The cilia greatly increase surface area of neuronal cell membrane at the nasal airspace, where inspired odors can interact with neuronal olfactory receptor proteins to activate specific neuron populations. The sustentacular cells are non-neuronal supporting cells, whose large cell bodies occupy the apical layer of the epithelium, sitting just beneath the neuronal cilia layer. Relatively understudied, sustentacular cells are known to be highly enriched in biotransformation enzymes of the cytochrome P450 family, and contribute to the ionic composition of the mucus layer surrounding the neuronal cilia.²⁶ Sustentacular cells may also have “glia-like” properties, exhibiting calcium responses to stimuli such as extracellular nucleotides.^{27,28} A thin cytoplasmic extension from the cell body of sustentacular cells extends basally, contacting the basal cells just above the epithelial basement membrane, likely providing feedback regulation of the basal cells.²⁹

The olfactory epithelium (Fig. 1) contains 2 categories of basal cells that normally function to replace mature epithelial cell types as needed, to maintain epithelial homeostasis. The globose basal cells function as active progenitors replacing neurons as needed, but also can function as reserve or upstream stem cells; the horizontal basal cells function as a dormant reserve stem cell activated by severe epithelial damage to reconstitute olfactory populations.³⁰⁻³² In addition, olfactory epithelium contains microvillar cells, interspersed apically among the sustentacular cells, which can express TRPM5 channels and may have sensory and regulatory roles. Microvillar cells, like the sensory neurons, arise from globose basal cells.³³ The ducts from submucosal Bowman’s glands also traverse the epithelium, secreting mucus to the epithelial surface. Finally, immune cells, especially macrophages, are interspersed within the olfactory epithelium. Axons from the olfactory neurons form fascicles in the lamina propria, which project through the cribriform plate of the ethmoid bone to synapse intracranially in the glomerular layer of the olfactory bulbs.

How the viral infection of sustentacular cells causes olfactory loss is a subject of ongoing study.³⁴ Another important question involves the pathogenesis of persistent olfactory loss in a subset of COVID-19 patients. In rodent models, Notch signaling appears necessary to maintain sustentacular cell expression of biotransformation enzymes, and loss of sustentacular cell Notch signaling led

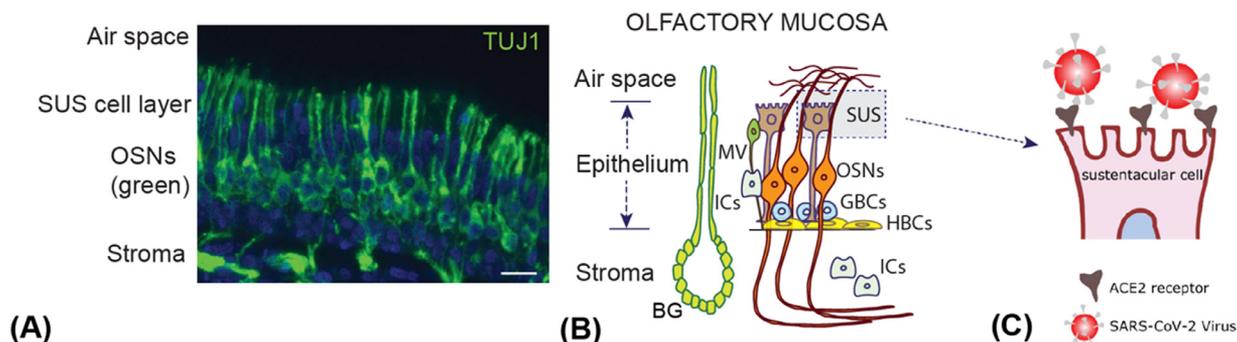


Fig. 1 SARS-CoV-2 infects olfactory sustentacular cells. (A) Organization of the olfactory epithelium, lining the superior portions of the nasal cavity. Human olfactory biopsy stained with antibody TUJ1 (green) outlining olfactory sensory neurons (OSNs); sustentacular cell (SUS) nuclei are located superficial to OSNs, near the nasal airspace. Nuclei are labeled in blue with DAPI; Bar approximately 10 μm . (B) Schematic showing olfactory cell populations, including sustentacular cells (SUS), olfactory sensory neurons (OSNs), globose basal cells (GBCs), horizontal basal cells (HBCs), microvillar cells (MV), immune cells (ICs), and Bowman's glands (BG). (C) The SARS-CoV-2 spike protein binds to the ACE2 surface receptor on sustentacular cells, permitting viral entry; cleavage of the spike protein likely occurs via the cell surface protease TMPRSS2 (not shown). (Color version of figure is available online.)

to some degree of olfactory neuronal cell death.³⁵ It is possible that a rapid and transient loss of some sustentacular cells due to SARS-CoV-2 infection could disrupt neuronal function and/or survival, causing transient anosmia (Figs. 1B, C and 2A). Alternatively, it is clear that a hallmark of COVID-19 is the inflammatory response that can accompany viral infection, and local inflammation likely contributes to post-COVID-19 olfactory disorders.

Inflammation

In mouse models, experimentally induced inflammation, using TNF α , can impair olfactory function, as identified in electro-olfactogram recordings.³⁶ Furthermore, prolonged inflammation leads to olfactory neuron cell death and, importantly, can impair the normal epithelial reconstitution by basal cells.³⁷ An analysis of olfactory mucosa from humans with aging-related olfactory loss (presbyosmia) identified inflammation-associated changes in basal stem cells, suggesting that similar mechanisms as described in mouse models may be involved in some forms of human olfactory disorders.³⁸ Given that COVID-19 is associated with a severe immune response, it is likely that inflammatory mechanisms contribute to acute or chronic olfactory loss. Indeed, in autopsies from subjects who died following acute COVID-19, olfactory neuron chromatin structure changes and accompanying gene expression alterations were identified.³⁹ Utilizing the hamster SARS-CoV-2 infection model, similar alterations were identified, along with evidence that local inflammation can drive these changes. Together, existing findings suggest a working model centering on local olfactory inflammation as a key driver of anosmia in COVID-19 (Fig. 2B). However, important questions remain regarding the pathobiology of persistent PASC olfactory dysfunction, requiring ongoing research to ultimately develop novel therapies.

Clinical evaluation

The ongoing COVID-19 pandemic has brought olfactory dysfunction into the spotlight of public attention, leading to an influx of patients with olfactory disturbances to otolaryngology clinics. Although olfactory dysfunction is a hallmark symptom of COVID-19, there is a range of clinical disorders that can contribute to olfactory dysfunction and appropriate workup is necessary to rule out treatable causes of olfactory dysfunction in the patient who presents with a chief complaint of olfactory disturbance.⁴⁰

The most common causes of olfactory dysfunction are active sinonasal disease, prior head trauma, and prior viral upper respiratory infection. Like hearing loss, olfactory loss can be categorized as conductive, sensorineural, or mixed. Conductive olfactory loss results from the disruption of airflow to the olfactory cleft, whereas sensorineural causes are secondary to direct damage to olfactory neurons or central pathways involved in higher order processing of odor perception. Given the mechanisms described in the previous section, it is likely that the COVID-19 related olfactory loss is sensorineural. Regardless of the etiology of the olfactory dysfunction, initial work-up is the same, with the goal to identify any correctable causes of olfactory dysfunction and initiate treatment as appropriate based on the diagnosis.

First, it is critical to obtain a thorough history of the patient's symptoms and their ongoing medical problems. Clinicians should inquire about the onset of olfactory dysfunction, associated symptoms, changes to medical history, and current medications or supplements. The patient's characterization of the olfactory dysfunction should also be ascertained to better assess their ability to detect, discriminate, and identify odors. Additionally, patients who complain of "taste loss" should also be queried to clarify whether they have a true ageusia/hypogeusia or whether they have lost flavor perception due to poor olfaction.

Olfactory testing should be administered to all patients with a chief complaint of olfactory dysfunction. There are

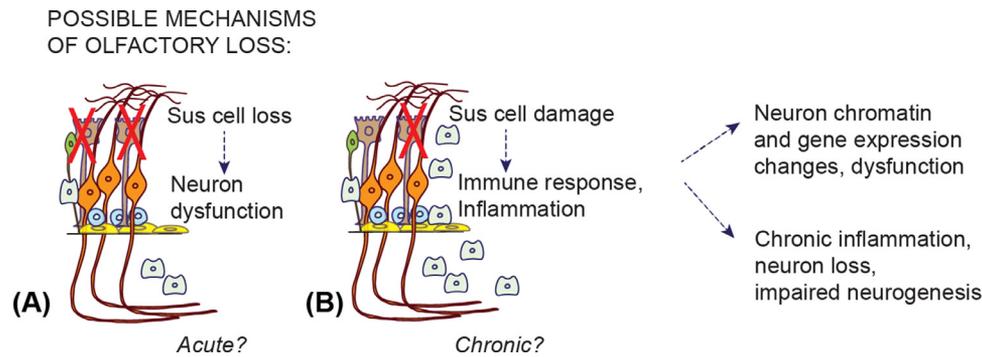


Fig. 2 Possible mechanisms of olfactory loss due to SARS-CoV-2 infection. (A) Following viral infection of sustentacular cells, olfactory loss may occur due to sustentacular cell death, impairing neuronal function. (B) Sensory loss could also occur due to immune cell response causing inflammation, neuronal dysfunction, or neuronal death and impaired epithelial reconstitution due to chronic inflammation. (Color version of figure is available online.)

validated psychophysical tests that can be easily administered in clinic, including the Smell Identification Test (SIT, Sensonics, Haddon Heights, NJ) and the Sniffin' Sticks (Burghart GmbH, Wedel, Germany). These tests can classify patients as normosmic, hyposmic, or anosmic. Taste strips are also available to assess gustatory function. More complex olfactometry or electrophysiologic testing is generally only done in a research setting.

As part of the physical exam, patients should also be evaluated with nasal endoscopy, with particular attention to the olfactory cleft region. In patients with conductive olfactory loss, endoscopy may reveal evidence of obstruction, such as structural deformities limiting airflow, inflammation or mucosal edema, mucous or pus, nasal polyps, or other intranasal masses. Evidence of objective olfactory loss with no obvious endoscopic findings suggests olfactory dysfunction of sensorineural origin. In such cases, radiographic studies such as computed tomography (CT) or magnetic resonance imaging (MRI) of the head may be considered to assess for intracranial lesions or occult paranasal sinus disease.

Treatment options for persistent hyposmia/parosmia

Currently, there are no specific drug therapies for sensorineural olfactory losses, including COVID-19. A majority of patients, perhaps 85%, will recover within 1 month of onset. However, given the number of people infected with SARS-CoV-2 worldwide, a substantial number of subjects will have prolonged olfactory dysfunction. It is important to counsel patients on safety issues with smoke, natural gas, and possibly spoiled food. Also, it is important to dissuade the use of unproven therapies, which may cause harm.

A recent consensus statement on the treatment for postviral olfactory dysfunction was only able to make quite limited recommendations, with no specific pharmacotherapies identified.¹⁸ Olfactory training therapy was recommended, which involves the intentional sniffing of odors twice daily in an effort to promote neuronal recovery.⁴¹

While it is considered risk-free, it is important to note that hyposmics rather than anosmics are most likely to derive benefit from olfactory training. Totally anosmic subjects who are repeatedly encouraged to “try harder” to continue olfactory training, despite no odor perception or improvement, may well be at risk for exacerbation of depression or other affective components that accompany anosmia.

Steroids are potent anti-inflammatories, so there is interest in the use of these medicines for COVID-19 anosmia. There is limited evidence to support systemic steroid use for COVID-19 olfactory loss, and systemic side effects limit utility. However, steroids can be administered via topical intranasal delivery, avoiding systemic side effects. While large formal studies have not evaluated topical nasal steroids post-COVID-19, a small preliminary report failed to identify improvement using mometasone nasal spray.⁴² It is important to consider delivery techniques, and difficulty depositing nasal sprays adequately to the olfactory cleft, which may limit efficacy. Also, properly powered studies focused on specific patient subsets, such as PASC hyposmic or parosmic subjects at specific timepoints post onset, with optimal delivery, may be required to draw adequate conclusions.

Among other potential therapies that have been evaluated for postviral olfactory disorders, intranasal theophylline has been found to be ineffective.⁴³ Evidence supporting minocycline is also lacking.^{18,44} The use of intranasal vitamin A is being actively studied. Vitamin A is a retinoid, and retinoic acid has regulatory effects on olfactory neurogenesis and regeneration,^{45,46} suggesting a potential mechanism for therapeutic utility.

To address the paucity of effective treatment modalities, there is an urgent need for investigations to better understand mechanisms and identify therapeutic options for individuals with COVID-19 related olfactory dysfunction.

Many patients have turned to organized groups founded by individuals suffering from olfactory dysfunction. Organizations such as Fifth Sense, AbScent, and Smell and Taste Association of North America (STANA) have developed educational materials, support groups and advocacy for those suffering from olfactory and taste dysfunction.

Moving forward, otolaryngologists may also be increasingly more involved in public education and awareness regarding olfactory sensory loss.

Disclosure

The author declare no conflicts of interest.

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