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REVIEW ARTICLE

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Long-term olfactory loss post-COVID-19: Pathobiology and potential therapeutic strategies

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Abstract

An acute loss of smell emerged as a striking symptom present in roughly half of the people infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus in the early phases of the COVID-19 pandemic. In most COVID-19 patients, olfaction recovers over the course of a few weeks. However, a lasting partial or complete loss of smell, often associated with distorted olfactory perceptions termed parosmia, has emerged as a widespread problem impacting at least 5%–10% of those who experience anosmia due to COVID-19. Our inability to offer effective therapies to this hyposmic or anosmic population, comprising millions of patients, highlights an enormous unmet need for the medical system. Here, we summarize the current understanding of the pathobiology causing acute olfactory loss due to SARS-CoV-2 infection, focusing on how the virus interacts with the peripheral olfactory system, a major site of viral infection. We also explore the problem of long-COVID olfactory dysfunction, which may accompany other persistent systemic disorders collectively termed postacute sequelae of COVID-19. Specifically, we discuss an emerging model focused on unresolved immune cell activity driving ongoing dysfunction. Finally, we review current and future therapeutic approaches aimed at restoring olfactory function.

KEYWORDS

hyposmia, inflammation, long-COVID, parosmia

Key points

- In this review we present current research investigating mechanisms of acute and long-COVID hyposmia and parosmia, highlighting immune-mediated changes of the olfactory epithelium.
- Several treatment strategies to restore olfactory function have targeted a diverse array of mechanisms, with limited success.

INTRODUCTION

Postviral olfactory dysfunction is one of the leading causes of anosmia, making up about 20%–30% of olfactory disorders, alongside traumatic brain injury, sinonasal inflammatory processes, as well as neurodegenerative disease. Intact olfactory function supports important functions, such as detection of noxious odors and spoiled foods. Disruption can have a profound negative impact on nutritional intake, social interactions, and has been linked to social isolation, mood disorders, and cognitive decline.[1] The incidence of postviral olfactory dysfunction has increased significantly with the COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019. While reports have been variable, prior studies have estimated approximately half of COVID-19 patients (especially during early variants of SARS-CoV-2) endorse olfactory deficits. Although many do recover their sense of smell, up to 10% of subjects report persistent olfactory dysfunction 6 months after infection. A recent cohort study following nearly 100 COVID-19 patients from 2020 onward measured olfactory function at the acute phase of infection, and 1, 2, and 3 years post-COVID-19. A majority of participants experienced olfactory dysfunction in the acute phase, but recovered by 2 years postinfection, while 14% had persistent olfactory dysfunction at 3 years postinfection.[2]

The olfactory epithelium is the peripheral chemosensory organ for smell detection and consists of several cell types: primary olfactory sensory neurons responsible for odor detection, basal stem cells that function to replace neurons following injury, and a barrier layer of sustentacular or supporting cells (Figure 1A). Basal stem cells are further divided into long-lived horizontal basal cells that act as a dormant reservoir that can be activated to differentiate into globose basal cells, which are the main proliferative population contributing to the regeneration of olfactory receptor neurons.[3,4] These cells make up the surface neuroepithelium located along the superior aspect of the nasal septum and medial lamellae of the superior turbinates. Beneath the surface epithelium is the lamina propria, which consists of stromal tissue and houses Bowman's glands, olfactory nerve axonal bundles, blood vessels, as well as cells of the immune system, largely CD45+ monocytes and lymphocytes,[5] though this immune population can also be seen infiltrating the epithelium in certain pathologies.

The process of basal cell activation and differentiation is tightly regulated and influenced by the surrounding cellular environment, including the local and recruited immune populations. Immune cell populations, and their appropriate regulation, support critical protective functions, as the olfactory epithelium serves as both a barrier epithelium and a sensory organ. For instance, in a mouse model of persistent olfactory inflammation, acute inflammation via tumor necrosis factor-alpha (TNFα)/nuclear factor kappa B signaling pathway helps induce proliferation and differentiation within the olfactory mucosa as well as promote a neutrophilic response. However, a chronic inflammatory state induced by prolonged TNF signaling halted basal cell differentiation and led to upregulation of pro-inflammatory cytokines interleukin (IL)1β and IFNγ, and shifted chemokine production to predominantly CCL19/20 to promote macrophage and dendritic cell migration and ultimately generate a T cell-dominated response.[6] In this review, we aim to present recent

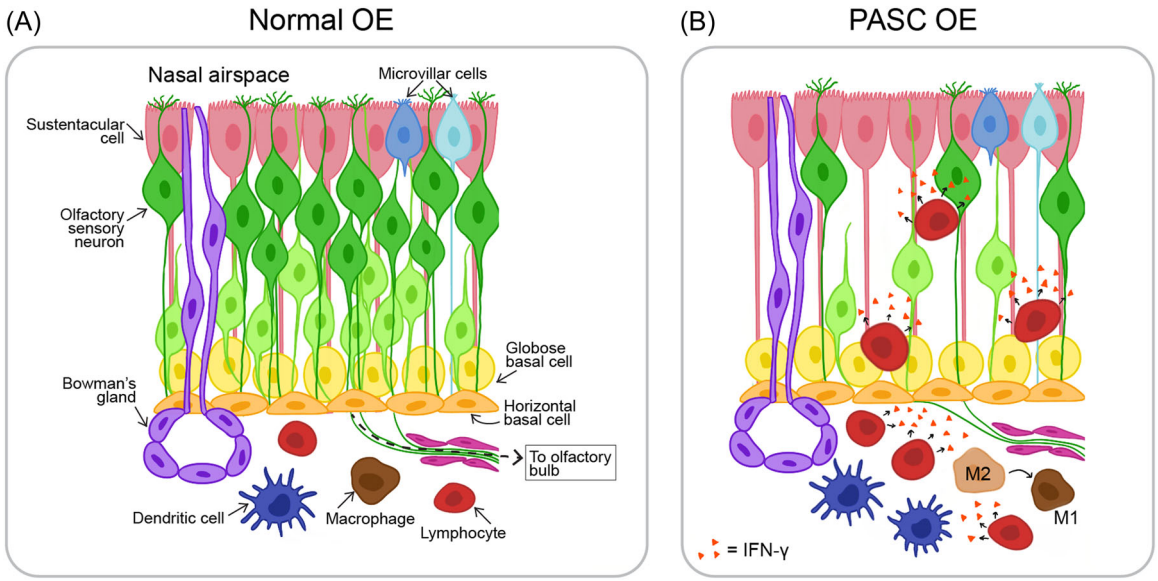

FIGURE 1 Schematic of the olfactory epithelium (OE) under (A) normal and (B) long-COVID hyposmic conditions; long-COVID medical disorders have been termed postacute sequelae of COVID-19 (PASC). (A) The normal OE contains diverse cell types originating from basal stem cells, with mature olfactory sensory neurons projecting their axons (green) through the basal lamina and up to the olfactory bulb. Occasional immune cells are present in the lamina propria. (B) In PASC hyposmic patients, increased immune infiltration is present both in the lamina propria and within the OE. Major inflammatory components include interferon (IFN)γ producing lymphocytes (red), a decrease in anti-inflammatory M2 macrophages, and an increase in $CD207^{+}$ dendritic cells.

discoveries and insights into SARS-CoV-2-mediated mechanisms of olfactory damage and smell loss and discuss current and future considerations for therapeutic strategies.

PATHOBIOLOGY OF ANOSMIA/HYPOSMIA IN ACUTE SARS-COV-2 INFECTION

SARS-CoV-2 readily enters the nasal airway. Early in the pandemic, it was observed that a majority of people experienced anosmia, or loss of smell, in the acute phase of infection.[7] This led to much speculation on the mechanisms leading to anosmia and concern over whether the virus infects neurons or potentially infects the brain. SARS-CoV-2 relies on cell-surface angiotensin-converting enzyme 2 (ACE2) and the serine protease TMPRSS2 for effective entry into host cells.[8,9] Initial studies utilizing single-cell RNA sequencing (scRNA-Seq) and immunohistochemistry from human and mouse tissues revealed that olfactory sensory neurons across species lacked expression of both key viral entry genes. Rather, neighboring sustentacular support cells, along with respiratory epithelial cells, were noted to have high expression of both genes, pointing toward a nonneuronal mechanism of anosmia.[10]

Subsequent work visualizing the infection process in human autopsy tissue using immunostaining and RNA in situ hybridization expanded upon these findings. Khan et al.[11] developed a protocol to rapidly collect olfactory tissue from the olfactory mucosa in the nasal cavity and olfactory bulb of the brain within hours following death from acute SARS-CoV-2 infection. The authors analyzed tissue from 85 cases and confirmed that sustentacular cells are the main cells infected by SARS-CoV-2 in the olfactory epithelium. They did not find evidence for viral infection of olfactory sensory neurons or any cells within the olfactory bulb, further supporting the notion that, at least in the case of early SARS-CoV-2 variants, acute anosmia is driven by infection of nonneuronal cells in the olfactory epithelium of the nose, without infection in the brain.[11]

Although olfactory sensory neurons are not directly infected by the virus, their function and/or survival must be altered following widespread infection of their neighboring support cells. Using a Syrian golden hamster model of SARS-CoV-2 infection to explore acute olfactory pathobiology, viral infection led to rapid alterations in the chromosomal architecture of olfactory sensory neurons, with a decrease in expression of olfactory receptors and odor transduction machinery.[12] The hamster model is useful because, unlike mouse, the wild-type SARS-CoV-2 spike protein can recognize the hamster ACE2 receptor, permitting infection without genetically altering the virus or the host animal. Furthermore, UV-neutralized serum taken from infected hamsters and injected into the nose of healthy hamsters was able to recapitulate these changes. Similar gene changes were observed in bulk RNA-Seq experiments in a human cohort of patients with acute SARS-CoV-2 infection. These data support a model in which acute sustentacular cell infection leads to severe local inflammation, resulting in cytokine exposure that can drive transcriptomic rearrangements in olfactory sensory neurons causing functional impairment.[12] In addition, widespread neuronal cell death secondary to ongoing inflammation occurs.

As newer variants of SARS-CoV-2 have emerged, including omicron subvariants, clinical presentations and illness severity have shifted, including decreased incidence of olfactory dysfunction.[13,14] It has been suggested that newer variants might utilize alternate viral entry genes on the host cell surface, or are capable of olfactory sensory neuron infection and/or spread to the central nervous system. Indeed, self-reported neurological symptoms following COVID-19 infection, including lasting or "long-COVID" sequelae, are widely reported.[15] Interestingly, in Syrian hamsters inoculated intranasally with high amounts of SARS-CoV-2, all four strains tested (original, Gamma, Delta, Omicron) led to detectable virus in the olfactory bulb, even though their effects on olfactory function differed. However, when the same study attempted to infect human neural stem cells in vitro with the four different variants, neurons were only able to be infected when they were engineered to artificially overexpress the two known SARS-CoV-2 entry genes ACE2 and TMPRSS2.[16,17] A comprehensive assessment of the acute course of infection in olfactory tissue across newer variants in vivo in humans failed to find evidence for neurotropism or neuroinvasion in the olfactory epithelium, along the olfactory nerve, or in the olfactory bulbs. Furthermore, the authors identified $p75NTR^{+}$ perineural olfactory nerve fibroblasts to be a previously underappreciated barrier protection against SARS-CoV-2.[18] Together, these studies highlight key differences between the hamster model utilized to study SARS-CoV-2 infection and acute infection in humans. While the hamster model remains an important resource, available evidence suggests that, in humans, SARS-CoV-2 variants are not likely capable of infecting olfactory sensory neurons or the olfactory bulb.

PATHOBIOLOGY OF ANOSMIA/HYPOSMIA IN LONG-COVID

Most individuals with COVID-induced olfactory loss recover olfactory function within 4 weeks following acute SARS-CoV-2 infection, but as many as 12% of people continue to experience a significantly decreased sense of smell, or persistent hyposmia/anosmia, for months to years after COVID-19 infection.[19] In fact, persistent olfactory dysfunction is among the most common symptoms reported in patients experiencing postacute sequelae of COVID-19 (PASC),[15] a term used to describe subjects exhibiting long-COVID symptoms lasting beyond 3 months postinfection. In the case of normal recovery, infected sustentacular cells are likely cleared, leading to epithelial regeneration of new cells from olfactory basal stem cells, in a well-described process supporting lifelong olfactory epithelial maintenance and repair.[4,20] In contrast, the cellular basis of PASC hyposmia in humans has been largely undefined until recently.

To address these questions, a recent study collected olfactory epithelial biopsies from live human subjects with clinically diagnosed PASC hyposmia and normosmic controls, based upon objectively confirmed olfactory function with psychophysical testing via the

Smell Identification Test (Sensonics Inc.). Olfactory tissue was then analyzed by single-cell transcriptomics and immunohistochemistry.[21] Across all PASC tissue, there was no evidence for persistent viral infection at the RNA or protein level. However, there was a striking increase in T cells in the olfactory epithelium and adjacent lamina propria in PASC hyposmic individuals. scRNA-Seq revealed enrichment of a specific CD8+ T cell population producing pro-inflammatory cytokines, including IFNγ. Other immune shifts, including an increase in $CD207^{+}$ dendritic cells and a decrease in anti-inflammatory M2 macrophages, were also evident in COVID PASC individuals. While sustentacular cells did not have differing levels of genes involved in active viral infection, there was significant upregulation of antigen processing machinery compared to normosmic controls. There was also a pattern of increased pathogen response genes in sustentacular cells that mirrored findings in a Syrian golden hamster model of PASC.[22] Interestingly, olfactory sensory neuron gene expression appeared largely unchanged between PASC hyposmic individuals and controls. However, there were significantly fewer olfactory sensory neurons present throughout the PASC hyposmic epithelium.[21] These findings outline a potential pathobiological mechanism of PASC hyposmia: an unresolved pro-inflammatory T cell subset remains within the olfactory mucosa long after infection is cleared, impeding survival and regeneration of new olfactory sensory neurons, and leading to a decreased ability to detect/process the presence of odorants (Figure 1B).

Why and how this persistent inflammatory infiltrate remains in the olfactory epithelium in some individuals is an area of on-going research. It is tempting to speculate that this may represent an autoimmune-like processes whereby SARS-CoV-2 infection exposes the immune system to previously immune-privileged self-antigens. G-protein coupled receptors (GPCRs) have been described as a common target for autoimmune antibodies, and COVID-19 infection has been implicated in dysregulating the balance of such antibodies.[23–25] The largest family of GPCRs, olfactory receptors, could thus represent a potential autoimmune target, perpetuating long-term inflammation in the olfactory epithelium.

While the number of studies investigating prolonged hyposmia in COVID-19 patients is limited, earlier work investigating the role of the immune system in non-PASC hyposmia may provide useful insights. The presence of pro-inflammatory cytokines such as IL-6 has been reported to show a correlation with olfactory dysfunction.[26] IL-6 is dysregulated in a number of inflammatory diseases, and is widely produced by macrophages, dendritic cells, and T and B lymphocytes to mobilize the immune response, often serving to link the innate and adaptive immune system. It has therefore been considered as a candidate biomarker to assess severity of COVID-19 disease or olfactory function. Correlative studies associating IL-6 levels with olfactory dysfunction in the setting of acute COVID-19 infection are unclear: while IL-6 plasma concentrations are directly proportional to the severity of COVID-19 disease, it was not related to performance on the Connecticut Chemosensory Clinical Research Center test.[27] However, other reports suggested increased concentrations of IL-6 in venous blood and serum samples correlated with worse olfactory measures assessed by Sino-nasal outcome test-22 quality of life assessments or Sniffin' Sticks psychophysical testing.[28,29] Type 1 IFNs, another family of immunomodulatory cytokines that have been shown to regulate downstream cytokine signaling including IL-6, demonstrated a robust upregulation in the olfactory bulb of SARS-CoV-2-infected hamsters. Single-cell sequencing of postmortem olfactory tissue from human donors demonstrated enrichment of pro-inflammatory chemokines *CCL5*, *CCL8*, and *CXCR3* in the olfactory epithelium, and cytokines including *IL6*, *IL7*, and *IL4R* in the olfactory bulb.[22] Together, an ongoing pro-inflammatory milieu appears to be a hallmark of persistent postviral smell loss.

In addition to hyposmia and anosmia following COVID-19, parosmia, or an altered sense of smell to various stimuli, is commonly reported. Such distortions in olfaction are often profoundly unpleasant, with previously pleasant smells evoking foul perceptions such as a burning or rotten odor. Parosmia can severely impair normal dietary habits. Some studies estimate the prevalence of PASC parosmia to be as high as 40%, with the most common time of onset occurring 2.5 months postinfection.[30] It has been suggested that the onset of parosmia coincides with meaningful recovery from olfactory loss in patients with viral-induced olfactory dysfunction.[31] While the cellular mechanisms for PASC parosmia remain unclear, this finding is in line with the theory that parosmia is caused by a miswiring of olfactory sensory neuron projections up to specific glomeruli in the olfactory bulb as new neurons are generated.[32,33] It is not clear why such a miswiring would occur in a subset of individuals, but it is possible that persistent underlying inflammation may contribute to this process.[34] Alternative explanations include abnormal activation of specific primary olfactory neurons, or central alterations in the olfactory bulb or cortex.

Outside of olfactory dysfunction, recent publications have identified similar dysregulation of inflammatory mediators in PASC patients with a variety of symptoms.[35] A study comparing serum levels of immune populations and cytokine levels in patients with and without PASC, or symptoms lasting longer than 12 weeks, showed an elevated innate immune response, stably elevated levels of type 1 and 3 IFNs and IL6 at least 8 months after infection, as well as a lack of naïve B and T cells.[36] A separate longitudinal study following patients who tested positive for SARS-CoV-2 with a variety of initial presentations, also reported that IFNγ-producing CD4+ T cell populations in serum remained stable over 8 months. Higher concentrations of these T cells, along with higher antibody titers, correlated with increased severity of initial presentation of disease such as hospitalization. Among patients with symptoms that persist over 4 months, this study demonstrated a lower frequency of CD107a+ CD8+ T cells and a more rapid decline in IFNγ-producing CD8+ T cells.[37] Symptom severity correlated with increased autoantibody formation targeting immune-related proteins involved with lymphocyte function, activation, trafficking. When a mouse model of COVID-19 (keratin-18-driven expression of human angiotensin converting enzyme 2, or k18-hACE2) was pretreated with neutralizing antibodies against the interferon (IFN) receptor, the mice

developed worse symptoms than those receiving phosphate buffered saline control, including weight loss and death, implicating this immune pathway in COVID-related disease progression.[38] Though these studies are not specific to olfactory dysfunction, they may provide further clues to the biological mechanisms that underlie postacute sequelae of SARS-CoV-2 infection.

CURRENT AND FUTURE TREATMENT STRATEGIES

Despite the prevalence of olfactory dysfunction following SARS-CoV-2 infection, there are currently few treatment options available. Informed by our growing understanding of likely pathobiologic mechanisms underlying lasting COVID-19-induced olfactory loss, potential therapeutic options are being explored. Here, we review currently available data regarding treatment strategies, summarized in Table 1.

Platelet-rich plasma (PRP), an autologous product separated from whole blood, has been investigated as a potential treatment for olfactory disorders, including post-COVID-19 olfactory loss. While a mechanism of action has not been defined, PRP is thought to harbor pro-regenerative properties, potentially due to the presence of growth factors. A recent study reported findings from a prospective trial in which approximately 30 patients with persistent smell loss following COVID, determined by psychophysical test scores, were randomized to receive a series of either PRP or placebo injections into the olfactory cleft. Outcome measures including threshold, discrimination, and identification (TDI) and visual analog scale scores were collected 1 and 3 months following treatment. PRP treatment was found to be safe and tolerable, with no adverse events reported. A mild improvement in smell discrimination at 3 months post-treatment in patients receiving PRP was reported; there was no difference in smell identification or threshold between the two groups. Additionally, subjective improvement scores between PRP and placebo arms were not statistically different.[41] A European study also treated PASC hyposmic patients ($n = 30$) with PRP injection or no treatment. Similarly, they reported favorable safety profiles in the PRP arm. A mild improvement was observed in the TDI score of patients receiving PRP, but the lack of a proper placebo arm in the study makes this difficult to interpret.[43] Taken together, the evidence for the efficacy of PRP to improve olfactory function in PASC hyposmic individuals is limited. Several limitations exist regarding PRP, including the heterogeneity of the composition of individual preparations of this autologous product, the specific cellular target or molecular mechanism of action (i.e., immune cells, olfactory neurons, basal cells, etc.), dosage regimens, and biomarkers of efficacy. Another limitation is that, at present, PRP treatment is considered an out-of-pocket expense, greatly limiting its availability to many patients, should data supporting efficacy emerge.

Stellate ganglion nerve blocks with local anesthetics, which have previously been used in the context of posttraumatic stress disorder,

TABLE 1 Summary of selected recent trials investigating therapeutic strategies for long-COVID hyposmia/parosmia and their outcomes.

Treatment	Study design	Outcome	Reference
Olfactory training therapy	RCT	Improvement in SIT and subjective VAS regardless of accelerated vs classical OT	[39]
	Retrospective study	Improved TDI with modified OT	[40]
Platelet-rich plasma	RCT	PRP resulted in mild improvement in smell discrimination, but no difference in identification or threshold nor subjective improvement, versus placebo, at 3 months	[41]
	Single-armed treatment evaluation, no controls	Suggests safety	[42]
	Pilot prospective controlled study	Improvement in mean TDI score 1-month post-PRP injection compared to OT controls	[43]
Stellate ganglion nerve block	Case series	Limited conclusions	[44]
	Single-arm pilot study	No adverse events; improvement in SIT, ODOR scores noted at 1 month, warranting further controlled study	[45]
Theophylline nasal irrigation	RCT, Phase 2	No improvement in SIT score between treatment versus control groups at 6 weeks	[46]
Oral prednisolone	RCT	Only treated short-term (<12 weeks duration hyposmics post-COVID-19); no significant improvement in TDI between treatment group and control	[47]
Intranasal mometasone + OT	RCT	No significant benefit with adding intranasal mometasone to olfactory training	[48]

Abbreviations: ODOR, olfactory dysfunction outcomes rating; OT, olfactory training therapy; PRP, platelet-rich plasma; RCT, randomized controlled trial; SIT, Smell Identification Test; TDI, threshold, discrimination, identification test (Sniffin' Sticks); VAS, visual analog scale.

migraine, and complex regional pain syndrome to mitigate dysautonomia, have been proposed as a long-COVID hyposmia or parosmia treatment, largely based on case reports.[44,49] The injection is performed by anesthesiologists using ultrasound guidance, usually infiltrating lidocaine. A mechanism of action is not clear; the stellate is an autonomic ganglion, not directly innervating the peripheral olfactory structures. A recent single-arm prospective pilot study identified 20 patients with persistent smell loss at least 1 year after COVID-19 and investigated the effects of bilateral stellate ganglion blocks on recovery of olfactory function through the use of multiple smell tests, including Clinical Global Impression-Improvement Scale, SIT, and olfactory dysfunction outcomes rating 1 week and 1 month following treatment. Conclusions are limited by a lack of a control arm; however, participants demonstrated modest improvement in scores and subjective ability to smell compared to baseline.[45]

Olfactory training therapy, consisting of daily repeated intentional odor exposure over a period of several months, has been widely recommended.[39,50,51] Originally developed in an effort to treat sensorineural olfactory impairments from multiple etiologies including postviral, posthead trauma, or presbyosmia, this has been examined extensively.[52] Individual reports, as well as a meta-analysis, suggest that in certain groups there is evidence for slight improvement in odor TDI.[53] The groups most likely to exhibit improvements, however, are generally those that are likely to spontaneously recover function, such as younger subjects with milder loss of shorter duration. Olfactory training has also been trialed in PASC patients with parosmia, with limited success. One report compared olfactory training to controls and suggested that olfactory training improved parosmia at 9 months, as measured by the parosmia assessment scale.[40] A mechanism of action for olfactory training has not been defined. It has been speculated that activation of any responsive neurons could provide trophic support or synapse remodeling. Another theory involves the promotion of regenerative activity via activation of basal stem cell proliferation, although evidence for this is lacking. Given the absence of risk in performing olfactory training therapy, a trial is often recommended for patients presenting with PASC hyposmia or parosmic, despite strong evidence supporting efficacy.

Recent insights into the pathobiological mechanisms driving PASC hyposmia may provide a way forward.[21] The olfactory epithelium in PASC hyposmic individuals harbors a significant increase in pro-inflammatory T cells, along with a marked decrease in the olfactory neuron population, suggesting that an unresolved local inflammatory environment impairs neuroepithelial maintenance. Local application of therapies blocking inflammation may be a strategy to restore normal neuronal numbers and function. A recent randomized controlled trial of intranasal mometasone plus olfactory training compared to olfactory training alone did not report a significant difference in olfactory function, as measured by Sniffin' Sticks, after 3 months.[48] However, computational modeling of inhaled intranasal steroid delivery suggests that the majority of the drug remains in the inferior nasal cavity and does not efficiently reach the olfactory cleft, which may limit efficacy.[54,55] An alternative option is systemic administration of steroid: a recent randomized controlled trial in 115 patients comparing a group receiving 10-day course of 40 mg once daily prednisolone to a placebo group found no significant difference in olfactory function at 3 months follow-up (as measured by TDI and Sniffin' Sticks).[47] This study only assessed acute COVID smell loss, lasting <12 weeks. In the oral form of administration, it is possible that concentrations of steroid reaching the olfactory epithelium are insufficient to reduce inflammation, and the ability to increase or extend the steroid dose is limited by systemic side effects. The effect of local intranasal delivery of theophylline, a phosphodiesterase inhibitor hypothesized to promote axonal repair and olfactory neuronal signaling, was compared to control saline irrigations in patients endorsing COVID-related hyposmia for greater than 3 months. There was no significant difference in University of Pennsylvania smell identification test or questionnaire of olfactory disorders between the treatment groups.[46] Other approaches have included small studies using unregulated supplements or antioxidants, such as zinc or fish oil components, with limited effects observed.[56] A future strategy under consideration is targeted delivery of defined anti-inflammatory or pro-regenerative drugs, with known mechanistic actions, specifically to the olfactory epithelium.

CONCLUSIONS

COVID-19 continues to have a significant burden on the global population, with acute and chronic changes in olfactory function in some subjects. Basic and translational research has begun to provide needed mechanistic insights into the causes of acute and chronic post-COVID olfactory disorders. Currently, available therapies have had limited success in treating hyposmia, highlighting the need for the identification of specific therapeutic strategies.

AUTHOR CONTRIBUTION

All authors significantly contributed to and agree with the content of this manuscript in its current state.

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The authors declare no conflict of interest.

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ETHICS STATEMENT

The authors have nothing to report.

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REFERENCES

1. Pence TS, Reiter ER, DiNardo LJ, Costanzo RM. Risk factors for hazardous events in olfactory-impaired patients. *JAMA Otolaryngol Head Neck Sur*. 2014;140:951-955.
2. Boscolo-Rizzo P, Hummel T, Spinato G, et al. Olfactory and gustatory function 3 years after mild COVID-19—a cohort psychophysical study. *JAMA Otolaryngol Head Neck Sur*. 2024;150:79-81.
3. Monti Graziadei GA, Graziadei PPC. Neurogenesis and neuron regeneration in the olfactory system of mammals. II. Degeneration and reconstitution of the olfactory sensory neurons after axotomy. *J Neurocytol*. 1979;8:197-213.
4. Leung CT, Coulombe PA, Reed RR. Contribution of olfactory neural stem cells to tissue maintenance and regeneration. *Nature Neurosci*. 2007;10:720-726.
5. Mellert TK, Getchell ML, Sparks L, Getchell TV. Characterization of the immune barrier in human olfactory mucosa. *Otolaryngol Head Neck Surg*. 1992;106:181-188.
6. Chen M, Reed RR, Lane AP. Chronic inflammation directs an olfactory stem cell functional switch from neuroregeneration to immune defense. *Cell Stem Cell*. 2019;25:501-513.e5.
7. Borsetto D, Hopkins C, Philips V, et al. Self-reported alteration of sense of smell or taste in patients with COVID-19: a systematic review and meta-analysis on 3563 patients. *Rhinology*. 2020;58:430-436.
8. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*. 2003;426:450-454.
9. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181:271-280.e8.
10. Brann DH, Tsukahara T, Weinreb C, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *Sci Adv*. 2020;6:eabc5801.
11. Khan M, Yoo SJ, Clijsters M, et al. Visualizing in deceased COVID-19 patients how SARS-CoV-2 attacks the respiratory and olfactory mucosae but spares the olfactory bulb. *Cell*. 2021;184:5932-5949.e15.
12. Zazhytska M, Kodra A, Hoagland DA, et al. Non-cell-autonomous disruption of nuclear architecture as a potential cause of COVID-19-induced anosmia. *Cell*. 2022;185:1052-1064.e12.
13. Meng B, Abdullahi A, Ferreira IATM, et al. Altered TMPRSS2 usage by SARS-CoV-2 omicron impacts infectivity and fusogenicity. *Nature*. 2022;603:706-714.
14. Vihta KD, Pouwels KB, Peto TE, et al. Omicron-associated changes in SARS-CoV-2 symptoms in the United Kingdom. *Clin Infect Dis*. 2022;76:e133-e141.
15. Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell*. 2022;185:881-895.e20.
16. de Melo GD, Lazarini F, Levallois S, et al. COVID-19-related anosmia is associated with viral persistence and inflammation in human olfactory epithelium and brain infection in hamsters. *Sci Transl Med*. 2021;13:eabf8396.
17. de Melo GD, Perraud V, Alvarez F, et al. Neuroinvasion and anosmia are independent phenomena upon infection with SARS-CoV-2 and its variants. *Nat Commun*. 2023;14:4485.
18. Khan M, Clijsters M, Choi S, et al. Anatomical barriers against SARS-CoV-2 neuroinvasion at vulnerable interfaces visualized in deceased COVID-19 patients. *Neuron*. 2022;110:3919-3935.e6.
19. Boscolo-Rizzo P, Menegaldo A, Fabbris C, et al. Six-month psychophysical evaluation of olfactory dysfunction in patients with COVID-19. *Chem Senses*. 2021;46:bjab006.
20. Gadye L, Das D, Sanchez MA, et al. Injury activates transient olfactory stem cell states with diverse lineage capacities. *Cell Stem Cell*. 2017;21:775-790.e9.
21. Finlay JB, Brann DH, Abi Hachem R, et al. Persistent post-COVID-19 smell loss is associated with immune cell infiltration and altered gene expression in olfactory epithelium. *Sci Transl Med*. 2022;14:eadd0484.
22. Frere JJ, Serafini RA, Pryce KD, et al. SARS-CoV-2 infection in hamsters and humans results in lasting and unique systemic perturbations after recovery. *Sci Transl Med*. 2022;14:eabq3059.
23. Cabral-Marques O, Marques A, Giil LM, et al. GPCR-specific autoantibody signatures are associated with physiological and pathological immune homeostasis. *Nat Commun*. 2018;9:5224.
24. Akbarzadeh R, Müller A, Humrich JY, Riemekasten G. When natural antibodies become pathogenic: autoantibodies targeted against G protein-coupled receptors in the pathogenesis of systemic sclerosis. *Front Immunol*. 2023;14:1213804.
25. Cabral-Marques O, Halpert G, Schimke LF, et al. Autoantibodies targeting GPCRs and RAS-related molecules associate with COVID-19 severity. *Nat Commun*. 2022;13:1220.
26. Henkin RI, Schmidt L, Velicu I. Interleukin 6 in hyposmia. *JAMA Otolaryngol Head Neck Sur*. 2013;139:728-734.
27. Vaira LA, De Vito A, Deiana G, et al. Correlations between IL-6 serum level and olfactory dysfunction severity in COVID-19 patients: a preliminary study. *Eur Arch Otrhinolaryngol*. 2022;279:811-816.
28. Cazzolla AP, Lovero R, Lo Muzio L, et al. Taste and smell disorders in COVID-19 patients: role of interleukin-6. *ACS Chem Neurosci*. 2020;11:2774-2781.
29. Liang Y, Mao X, Kuang M, et al. Interleukin-6 affects the severity of olfactory disorder: a cross-sectional survey of 148 patients who recovered from Omicron infection using the Sniffin' Sticks test in Tianjin, China. *Int J Infect Dis*. 2022;123:17-24.
30. Hopkins C, Surda P, Vaira LA, et al. Six month follow-up of self-reported loss of smell during the COVID-19 pandemic. *Rhinology*. 2021;59:26-31.
31. Liu DT, Sabha M, Damm M, et al. Parosmia is associated with relevant olfactory recovery after olfactory training. *Laryngoscope*. 2021;131:618-623.
32. Christensen MD. Rhinotopy is disrupted during the re-innervation of the olfactory bulb that follows transection of the olfactory nerve. *Chem Senses*. 2001;26:359-369.
33. Liu ZY, Vaira LA, Boscolo-Rizzo P, Walker A, Hopkins C. Post-viral olfactory loss and parosmia. *BMJ Medicine*. 2023;2:e000382.
34. Gangadharan V, Zheng H, Taberner FJ, et al. Neuropathic pain caused by miswiring and abnormal end organ targeting. *Nature*. 2022;606:137-145.
35. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. 2023;21:133-146.
36. Phetsouphanh C, Darley DR, Wilson DB, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. *Nature Immunol*. 2022;23:210-216.
37. Peluso MJ, Deitchman AN, Torres L, et al. Long-term SARS-CoV-2-specific immune and inflammatory responses in individuals recovering from COVID-19 with and without post-acute symptoms. *Cell Rep*. 2021;36:109518.
38. Wang EY, Mao T, Klein J, et al. Diverse functional autoantibodies in patients with COVID-19. *medRxiv*. 2021;595:283-288.
39. Pires ÍAT, Steffens ST, Mocelin AG, et al. Intensive olfactory training in Post-COVID-19 patients: a multicenter randomized clinical trial. *Am J Rhinol Allergy*. 2022;36:780-787.
40. Altundag A, Yilmaz E, Kesimli MC. Modified olfactory training is an effective treatment method for COVID-19 induced parosmia. *Laryngoscope*. 2022;132:1433-1438.

41. Yan CH, Jang SS, Lin HFC, et al. Use of platelet-rich plasma for COVID-19-related olfactory loss: a randomized controlled trial. *Int Forum Allergy Rhinol*. 2023;13:989-997.
42. Lechien JR, Le Bon SD, Saussez S. Platelet-rich plasma injection in the olfactory clefts of COVID-19 patients with long-term olfactory dysfunction. *Eur Arch Otrhinolaryngol*. 2023;280:2351-2358.
43. Steffens Y, Le Bon SD, Lechien J, et al. Effectiveness and safety of PRP on persistent olfactory dysfunction related to COVID-19. *Eur Arch Otrhinolaryngol*. 2022;279:5951-5953.
44. Kalava A, Benyahia SA, Tico Calzada R, Staat CM. Efficacy of stellate ganglion block in treating long-term COVID-19-related olfactory and gustatory dysfunction: a case series. *Cureus*. 2023;15:e40929.
45. Peterson AM, Miller BJ, Kallogjeri D, et al. Stellate ganglion block for the treatment of COVID-19-induced olfactory dysfunction: a prospective pilot study. *Otolaryngol Head Neck Surg*. 2024;170:272-276.
46. Gupta S, Lee JJ, Perrin A, et al. Efficacy and safety of saline nasal irrigation plus theophylline for treatment of COVID-19-related olfactory dysfunction: the SCENT2 phase 2 randomized clinical trial. *JAMA Otolaryngol Head Neck Sur*. 2022;148:830-837.
47. Schepens EJA, Blijleven EE, Boek WM, et al. Prednisolone does not improve olfactory function after COVID-19: a randomized, double-blind, placebo-controlled trial. *BMC Med*. 2022;20:445.
48. Hintschich CA, Dietz M, Haehner A, Hummel T. Topical administration of mometasone is not helpful in post-COVID-19 olfactory dysfunction. *Life*. 2022;12:1483.
49. Chauhan G, Upadhyay A, Khanduja S, Emerick T. Stellate ganglion block for anosmia and dysgeusia due to long COVID. *Cureus*. 2022;14:e27779.
50. Patel ZM, Holbrook EH, Turner JH, et al. International consensus statement on allergy and rhinology: olfaction. *Int Forum Allergy Rhinol*. 2022;12:327-680.
51. Lechner M, Liu J, Counsell N, et al. The COVANOS trial—insight into post-COVID olfactory dysfunction and the role of smell training. *Rhinology*. 2022;60:188-199.
52. Hummel T, Rissom K, Reden J, Hähner A, Weidenbecher M, Hüttenbrink KB. Effects of olfactory training in patients with olfactory loss. *Laryngoscope*. 2009;119:496-499.
53. Turner JH. Olfactory training: what is the evidence. *Int Forum Allergy Rhinol*. 2020;10:1199-1200.
54. Basu S, Holbrook LT, Kudlaty K, et al. Numerical evaluation of spray position for improved nasal drug delivery. *Sci Rep*. 2020;10:10568.
55. Inthavong K, Ma J, Shang Y, et al. Geometry and airflow dynamics analysis in the nasal cavity during inhalation. *Clin Biomech (Bristol, Avon)*. 2019;66:97-106.
56. De Luca P, Camaioni A, Marra P, et al. Effect of ultra-micronized palmitoylethanolamide and luteolin on olfaction and memory in patients with long COVID: results of a longitudinal study. *Cells*. 2022;11:2552.

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