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Intranasal Insulin for Treatment of Persistent Post-COVID-19 Olfactory Dysfunction: A Scoping Review

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Abstract

Olfactory dysfunction has emerged as a prominent symptom of COVID-19, persisting in a subset of patients even after recovery. This scoping review aims to explore the potential of intranasal insulin as a treatment modality for persistent post-COVID-19 olfactory dysfunction. A comprehensive literature search was conducted to gather relevant studies examining the role of intranasal insulin in treating olfactory dysfunction, particularly in post-COVID-19 cases. Studies were included investigating intranasal insulin's mechanisms, efficacy, safety, and clinical outcomes. The review synthesizes findings from various studies suggesting the therapeutic potential of intranasal insulin in improving olfactory function. Research highlights the influence of intranasal insulin on neuroprotection, neurogenesis, and synaptic plasticity within the olfactory system, providing insights into its mechanisms of action.

Furthermore, preliminary clinical evidence suggests improvements in olfactory sensitivity and intensity following intranasal insulin administration in post-COVID-19 patients with persistent olfactory dysfunction. While initial findings are encouraging, further rigorous investigations, including clinical trials with larger cohorts, are essential to validate these observations, ascertain optimal dosage regimens, and establish the safety and efficacy of intranasal insulin. This review provides a foundation for future research directions aimed at harnessing the therapeutic potential of intranasal insulin in addressing olfactory dysfunction following COVID-19.

Keywords: Intranasal insulin, Olfactory dysfunction, Post-COVID-19, Regeneration, Neuroprotection

1. Introduction

The global Coronavirus disease 2019 (COVID-19) pandemic has presented a multifaceted health challenge, manifesting in a spectrum of clinical manifestations that extend beyond the acute phase of infection.[1] Notably, a substantial cohort of individuals recovering from COVID-19 continues to contend with persistent olfactory dysfunction, characterized by anosmia or hyposmia, significantly impacting their quality of life and daily functioning.[2–4] This enduring impairment in olfactory function following COVID-19 recovery has drawn attention as a lingering and often distressing sequelae of the viral infection. Amidst the search for viable therapeutic strategies, emerging evidence has spotlighted intranasal insulin as a potential avenue for ameliorating persistent post-COVID-19 olfactory dysfunction.[5,6] Intriguingly, insulin, recognized primarily for its role in metabolic regulation, harbors neuroprotective properties that hold promise for mitigating neurological complications, including impaired olfaction.[7]

The present scoping review seeks to comprehensively investigate and evaluate the existing literature

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about using intranasal insulin as a targeted therapeutic intervention for addressing persistent post-COVID-19 olfactory dysfunction. This review aims to synthesize and analyze available research studies, clinical trials, and empirical evidence, thereby delineating the efficacy, safety profile, underlying mechanisms of action, and potential limitations associated with intranasal insulin therapy in this context.

The intricate interplay between the pathophysiology of COVID-19 and the persistence of olfactory dysfunction, coupled with the therapeutic potential of intranasal insulin, underscores the critical need for a comprehensive understanding of this treatment approach. This scoping review endeavors to critically appraise current research, serving as a valuable resource for healthcare professionals, researchers, and clinicians involved in managing persistent post-COVID-19 olfactory dysfunction. By elucidating the literature's gaps, strengths, and limitations, this review aims to facilitate informed decision-making and stimulate further investigation, fostering the development of effective interventions for individuals grappling with this enduring consequence of COVID-19 infection.

2. Methods

The methodology employed for this scoping review involved a literature search of various electronic databases, including PubMed/MEDLINE, Embase, Cochrane Library, and Scopus, spanning publications from inception to November 2023. The search strategy utilized a combination of keywords and Medical Subject Headings (MeSH) terms related to “intranasal insulin,” “post-COVID-19 olfactory dysfunction,” “COVID-19 sequelae,” and “olfactory impairment,” refining search precision with Boolean operators. Inclusion criteria encompassed original research studies, clinical trials, and observational studies focusing on intranasal insulin as a therapeutic intervention for persistent post-COVID-19 olfactory dysfunction. Exclusion criteria involved conference abstracts and studies unrelated to intranasal insulin or not specifically addressing olfactory dysfunction in COVID-19. Two independent reviewers (J.M. and A.K.) conducted a rigorous screening of titles, abstracts, and full texts based on predefined criteria, resolving disagreements through discussion and consensus. A standardized data extraction form was utilized to systematically extract relevant information from selected studies, covering study design, participant characteristics, intervention details, outcomes, efficacy, safety, and limitations. The scoping review methodology did not involve a formal quality assessment or risk of bias analysis. Findings will be synthesized narratively to provide a comprehensive overview of the existing literature on intranasal insulin's role in addressing persistent post-COVID-19 olfactory dysfunction, aiming to highlight patterns, trends, and gaps in the evidence to guide future research and clinical considerations.

3. Pathophysiology of olfactory dysfunction post-COVID-19

The pathophysiology of olfactory dysfunction in post-COVID-19 recovery involves various factors affecting the olfactory system. Olfactory dysfunction, particularly anosmia or hyposmia, has emerged as a standard and persistent symptom in individuals following COVID-19 infection.[1] Several mechanisms contribute to the olfactory dysfunction observed in post-COVID-19 patients. Fig. 1 highlights the involved mechanisms of olfactory dysfunction after COVID-19 infection.

3.1. Viral invasion and damage

The entry of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into the body's cells involves a complex process facilitated by the spike protein on the virus and the angiotensin-converting enzyme 2 (ACE2) receptors on the surface of human cells.[8] While the respiratory tract is a primary site of infection, ACE2 receptors are expressed in various tissues throughout the body, including the olfactory epithelium, which lines the nasal cavity and is responsible for detecting smells. Viral particles can contact cells in the nasal cavity upon inhalation, including the olfactory sensory neurons and supporting cells.[9] These olfactory cells, expressing ACE2 receptors, become susceptible to viral invasion. The spike protein on the surface of the SARS-CoV-2 virus binds to ACE2 receptors on the cell membrane, facilitating the entry of the virus into these cells.[10] Once inside, the virus replicates and may induce cellular damage through several mechanisms. This viral replication can trigger an inflammatory response in the olfactory epithelium, leading to increased production of cytokines and chemokines, signaling molecules that attract immune cells to the site of infection.[11] This inflammation can cause swelling, disrupt normal cellular function, and ultimately result in cell death or damage. The damage inflicted upon the olfactory sensory neurons and supporting cells can disrupt the normal functioning of the olfactory system.[12] Olfactory sensory neurons are responsible for detecting odor molecules, and any

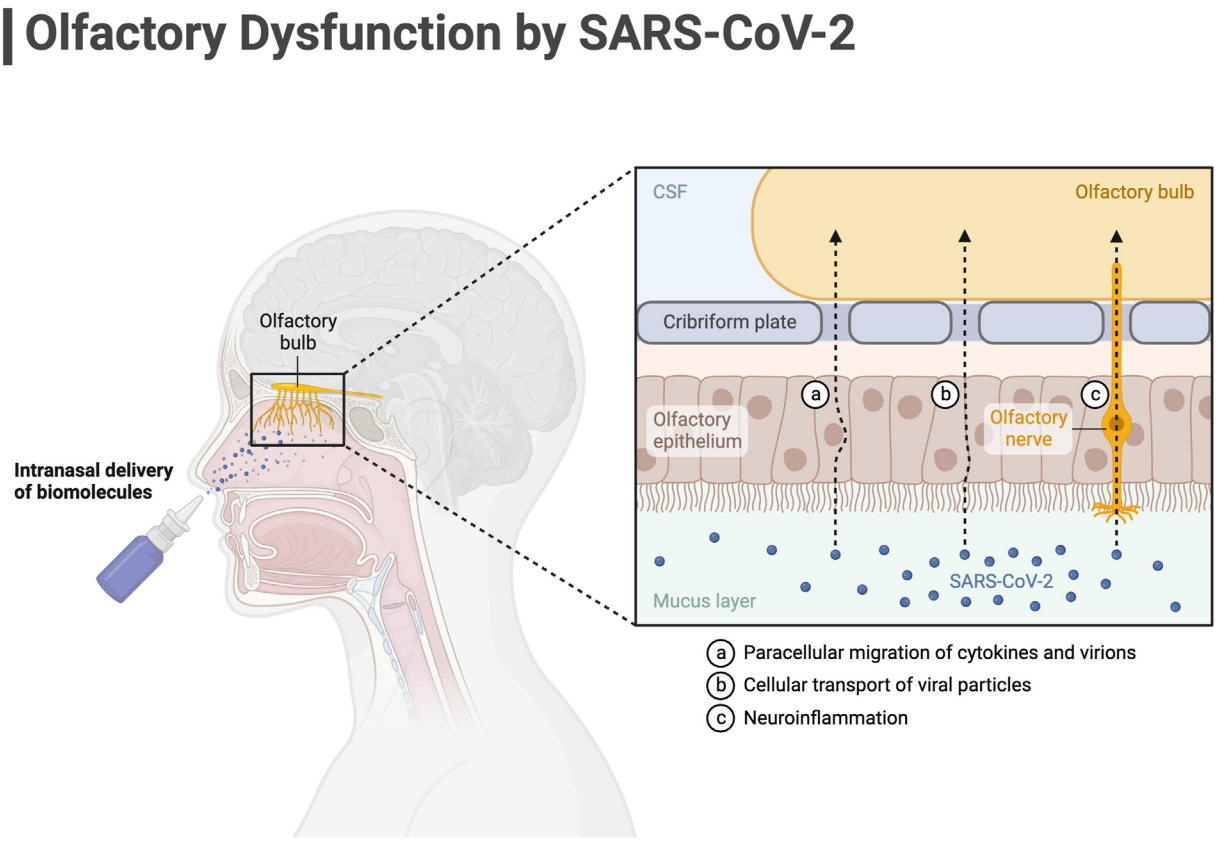

Fig. 1. Mechanism of olfactory dysfunction in SARS-CoV-2.

impairment or loss of these neurons can lead to anosmia or hyposmia, affecting an individual's ability to smell or perceive odors.[13] Furthermore, the damage caused by the virus may extend beyond direct cell destruction. It can lead to alterations in the olfactory epithelium's microenvironment, affecting the regenerative capacity of the olfactory sensory neurons and hindering the standard repair mechanisms.

3.2. Neuroinflammation and olfactory bulb involvement

When infected with SARS-CoV-2, the immune system responds by mounting an inflammatory reaction to combat the virus.[14] This immune response, which involves the release of cytokines and other inflammatory mediators, is essential for fighting the infection. However, in some cases, this response can become dysregulated, leading to excessive inflammation throughout the body, including the central nervous system (CNS), a phenomenon commonly referred to as neuroinflammation.[15–20] COVID-19 has been associated with neurological manifestations, suggesting that the inflammatory response triggered by the virus can extend to the CNS.[21] The olfactory bulb, located at the front of the brain, plays a pivotal role in processing olfactory information received from the olfactory sensory neurons in the nasal cavity.[22] It acts as a relay station, transmitting these signals to higher brain regions responsible for interpreting and identifying smells. In neuroinflammation cases, inflammatory molecules and immune cells can infiltrate the olfactory bulb.[23] This inflammatory response within the olfactory bulb can disrupt its normal function. The inflammatory process may lead to structural changes, neuronal damage, or alterations in the neural circuitry involved in olfactory signal transmission.[24]

Due to this inflammation in the olfactory bulb, the transmission of olfactory signals from the olfactory sensory neurons to the higher brain centers can be disrupted or impaired. This disruption in signal transmission interferes with the brain's ability to interpret and process olfactory information accurately, resulting in olfactory dysfunction.[25] Furthermore, the inflammatory milieu within the olfactory bulb may interfere with the regenerative capacity of neurons or affect the supportive cells, impacting the repair mechanisms crucial for maintaining normal olfactory function.[26] It's important to note that while neuroinflammation and involvement of the olfactory bulb in COVID-19-related olfactory dysfunction

are plausible mechanisms, the exact extent and specific pathways through which SARS-CoV-2 affects the CNS and olfactory bulb require further investigation.[27] Nonetheless, understanding the potential impact of neuroinflammation on the olfactory system sheds light on the complex mechanisms underlying post-COVID-19 olfactory dysfunction and highlights the importance of addressing neuroinflammatory processes in therapeutic approaches to restore olfactory function.[28]

3.3. Disruption of olfactory neural pathways

The olfactory system comprises a complex network of neural pathways that facilitate the transmission of olfactory information from the nasal cavity to higher brain regions responsible for processing and interpreting smells.[29] This intricate pathway involves a series of events starting with detecting odorant molecules by olfactory sensory neurons located in the olfactory epithelium of the nasal cavity. Upon exposure to odorants, olfactory sensory neurons initiate an electrical signal that travels along their axons through the cribriform plate, a bony structure in the skull, and reaches the olfactory bulb—a specialized structure at the base of the brain. In the olfactory bulb, these signals are processed, refined, and transmitted to interconnected brain regions, such as the olfactory cortex, limbic system, and higher cortical areas responsible for odor identification, memory, and emotional responses.[30] The disruption caused by viral-induced damage or inflammation can affect the neural connections and synaptic transmission within the olfactory system.[31] This interference in neural circuitry may disrupt the precise coding and interpretation of olfactory signals, leading to a distorted perception of smells or a diminished sense of smell. The consequence of these disruptions in olfactory neural pathways is the impairment of the brain's ability to interpret and process olfactory signals accurately.[32] Consequently, individuals recovering from COVID-19 may experience a loss, reduction, or alteration in their sense of smell, contributing to anosmia, hyposmia, or dysosmia.

4. Role of intranasal insulin in neuroprotection and regeneration

Beyond its primary role in glucose metabolism, insulin has been recognized for its potential neuroprotective effects, particularly in modulating inflammatory responses within the brain.[33] In viral infections such as SARS-CoV-2, the virus can induce an inflammatory cascade within the central nervous system, contributing to neuroinflammation that may lead to neuronal damage and dysfunction.[34] Insulin receptors are abundantly expressed in various brain regions, including those involved in olfactory processing.[35] Upon activation, these receptors can trigger signaling pathways that affect inflammatory processes within the CNS. Insulin's anti-inflammatory properties have been observed through several mechanisms.[36]

Insulin has been shown to modulate the production and activity of pro-inflammatory cytokines and chemokines in the brain.[37] It can downregulate the expression of inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), which are often elevated in neuroinflammatory conditions.[38] Microglia, the resident immune cells in the brain, play a crucial role in the brain's immune response.[39] Insulin can modulate microglial activation, reducing their pro-inflammatory responses and preventing the release of cytotoxic substances that can harm neurons during inflammation.[40] Insulin's anti-inflammatory effects are often linked to its ability to counteract oxidative stress. By reducing the production of reactive oxygen species (ROS) and enhancing the activity of antioxidant defense mechanisms, insulin can mitigate oxidative damage to neurons induced by inflammatory processes.[41] Insulin may help maintain the integrity of the blood–brain barrier (BBB), the protective barrier that regulates the passage of substances between the bloodstream and the brain.[42] Preserving BBB integrity prevents inflammatory cells and molecule infiltration into the brain parenchyma. Fig. 2 illustrates the mechanism of neurogenesis with insulin.

5. Literature review

The sudden loss of smell has emerged as a distinctive and prominent symptom of SARS-CoV-2 infection. Studies indicate that individuals reporting this sudden loss of smell are significantly more likely—17 times more—to test positive for COVID-19 compared to those without this specific symptom.[43] Olfactory dysfunction in COVID-19 patients varies widely, ranging from 8% to 85%, influenced by factors like age, health status, and virus variants.[44] Although many individuals typically recover their sense of smell within a month after contracting COVID-19, some experience persistent olfactory issues. Research suggests that around a quarter of patients face olfactory dysfunction even after six months post-infection.[45] As the SARS-CoV-2 pandemic extends, concerns are mounting regarding chronic olfactory dysfunction persisting beyond six

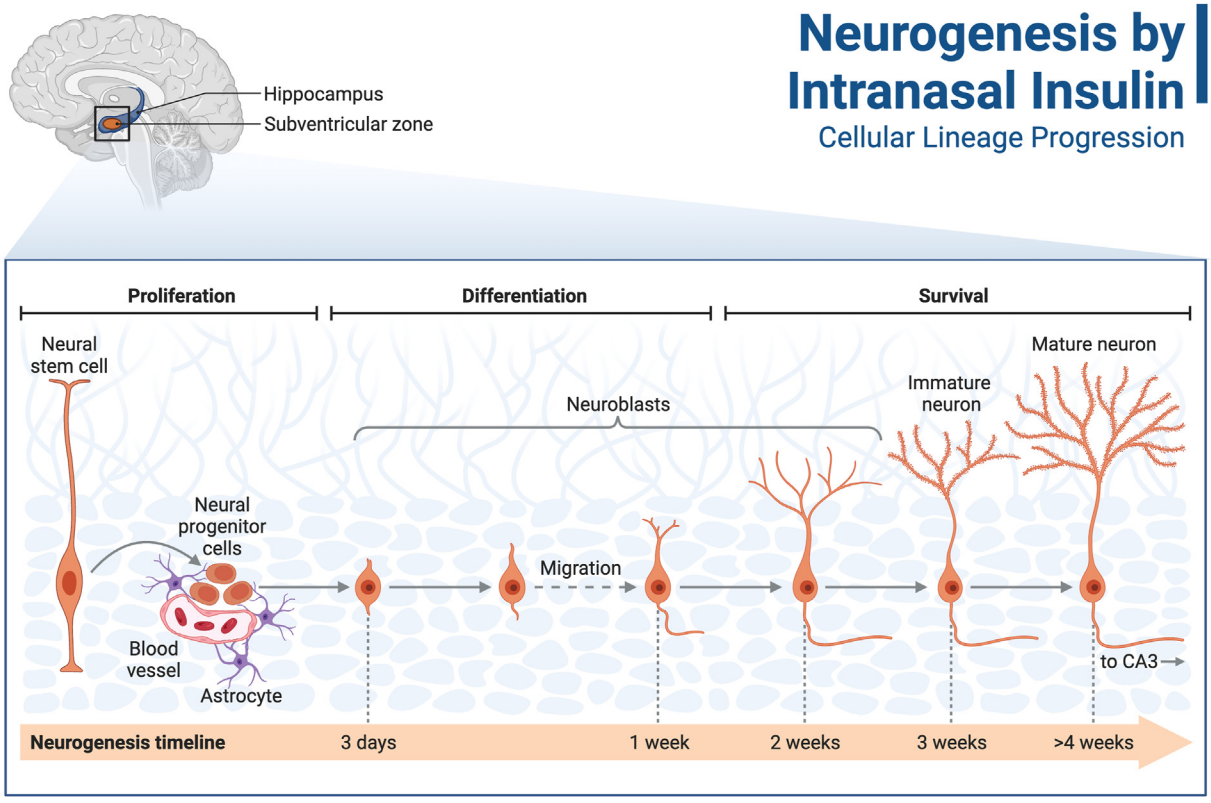

Fig. 2. Neurogenesis by insulin.

months, posing a potential public health challenge. Estimates indicate a significant increase in the number of individuals affected, with approximately 700,000 to 1.6 million people in the United States now grappling with this condition—a relative rise from 5.3% to 12% in the population.[46]

In a prospective interventional cohort study involving sixteen volunteers experiencing persistent olfactory dysfunction after SARS-CoV-2 infection, intranasal administration of neutral protamine Hagedorn (NPH) insulin demonstrated potential as a treatment for recalcitrant anosmia or severe hyposmia unresponsive to standard therapies.[5] The study evaluated olfactory function using the Chemosensory Clinical Research Center test of olfaction (COT) before and after the intervention, consisting of placing NPH insulin-soaked gelatin sponges into each olfactory cleft twice weekly for a month. Results showed significant improvements in qualitative, quantitative, and global COT scores (an increase of 1.53, 2.00, and 2.01 points, respectively), indicating enhanced olfactory function. Additionally, glycaemic blood levels decreased, suggesting the intervention's safety and tolerability.

Another study aimed to assess the effectiveness of intranasal insulin in treating hyposmia, a condition characterized by a reduced sense of smell, for which there are currently limited treatment options.[6] Conducted as a double-blinded, randomized controlled trial, the research involved 38 participants meeting specific criteria for hyposmia. Subjects were randomly assigned to receive either intranasal insulin gel foam or a saline-soaked gel foam (placebo) placed in the olfactory cleft through an endoscopic procedure, repeated twice weekly for four weeks. Olfactory function was evaluated using the Connecticut Chemosensory Clinical Research Center score before and after treatment. The study revealed a notable improvement in the olfactory sense among participants receiving intranasal insulin compared to the placebo group after four weeks, with no reported adverse effects in either group. These findings suggest that intranasal insulin administration at 40 IU could enhance olfactory function without significant side effects in this small cohort.

In another study, investigators explored the impact of intranasal insulin on olfactory function in ten patients experiencing post-infectious olfactory loss.[7] Previous research has suggested connections between intranasal insulin application and improved memory, reduced food intake, and heightened olfactory thresholds in healthy individuals. Additionally, certain health conditions

associated with central nervous system insulin resistance, like type II diabetes, Alzheimer's disease, and obesity, have shown links to impaired odor recognition. Our study involved administering 40 IU of intranasal insulin or a placebo to these patients and conducting olfactory performance tests before and after administration. After insulin administration, the results immediately enhanced olfactory sensitivity, intensity ratings, and odor identification accuracy. Notably, patients with higher body mass index showed improved performance in identifying odors. These findings highlight the potential relationship between cerebral insulin levels and impaired sense of smell.

6. Safety profile of intranasal insulin

The safety profile of intranasal insulin has been a subject of interest, particularly concerning potential adverse effects associated with its administration. While research has indicated promising therapeutic benefits in various conditions, including olfactory dysfunction, understanding its safety is crucial. Studies evaluating intranasal insulin have generally reported a favorable safety profile.[47] Commonly noted adverse effects are mild and transient, predominantly involving local reactions at the administration site, such as nasal irritation, itching, or mild discomfort.[48] These effects tend to diminish with continued use and are often well-tolerated. However, some individuals may experience less common adverse effects, including mild headaches, alterations in taste perception, or nasal congestion. Systemic side effects are rare but have been reported in some cases, such as changes in blood glucose levels, particularly in individuals predisposed to hypoglycemia.[48]

Additionally, individuals with underlying medical conditions, such as diabetes or other metabolic disorders, might require careful monitoring due to the potential influence of intranasal insulin on blood glucose levels. It's important to note that intranasal insulin's safety and adverse effect profile may vary depending on factors such as dosage, frequency of administration, individual sensitivity, and underlying health conditions.[48] Therefore, careful monitoring and proper medical supervision are essential when considering intranasal insulin as a therapeutic intervention.

7. Future directions

One critical area for future research involves determining the optimal dosage, frequency, and duration of intranasal insulin administration to maximize its efficacy while minimizing potential side effects. Rigorous clinical trials with larger sample sizes and extended follow-up periods are needed to establish this therapy's long-term safety and sustained effectiveness. Investigating how intranasal insulin affects different patient populations and identifying specific subgroups that may benefit most from this treatment will be crucial in advancing personalized medicine approaches for olfactory dysfunction. Moreover, bridging the gap between research findings and clinical application is essential. Developing standardized protocols and guidelines for healthcare practitioners could facilitate the effective implementation of intranasal insulin therapy in treating olfactory dysfunction.

Additionally, exploring combination therapies that integrate intranasal insulin with other modalities, such as rehabilitation techniques or adjunct medications, may offer synergistic effects, potentially enhancing olfactory recovery in affected individuals. Beyond olfactory dysfunction, exploring the broader application of intranasal insulin in related neurological conditions, such as neurodegenerative diseases or metabolic disorders, could reveal its potential as a disease-modifying intervention. Efforts to translate research findings into clinical practice are vital to expand treatment options and improve the quality of life for individuals affected by olfactory dysfunction and related neurological issues. Overall, continued research efforts and comprehensive investigations are necessary to unlock the full therapeutic potential of intranasal insulin in addressing olfactory dysfunction and associated neurological disorders.

8. Conclusion

In conclusion, intranasal insulin emerges as a promising therapeutic avenue for addressing olfactory dysfunction, offering potential improvements in olfactory sensitivity and intensity ratings among individuals experiencing post-infectious olfactory loss. This review highlights immediate enhancements in olfactory performance following intranasal insulin administration, suggesting its influence on olfactory sensitivity and odor identification accuracy. The findings underscore the possible connection between cerebral insulin levels and impaired sense of smell, providing valuable insights into the mechanisms underlying olfactory loss. These insights pave the way for future research endeavors to refine treatment protocols and leverage intranasal insulin as a potential therapeutic intervention for individuals grappling with persistent olfactory challenges.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Almas T, Malik J, Alsubai AK, et al. Post-acute COVID-19 syndrome and its prolonged effects: an updated systematic review. *Ann Med Surg (Lond)*. 2022 Aug;80:103995. http://dx.doi.org/10.1016/j.amsu.2022.103995. Epub 2022 Jun 15. PMID: 35721785; PMCID: PMC9197790.
2. Doty RL. Olfactory dysfunction in COVID-19: pathology and long-term implications for brain health. *Trends Mol Med*. 2022 Sep;28(9):781–794. http://dx.doi.org/10.1016/j.molmed.2022.06.005. Epub 2022 Jun 20. PMID: 35810128; PMCID: PMC9212891.
3. Las Casas Lima MH, Cavalcante ALB, Leão SC. Pathophysiological relationship between COVID-19 and olfactory dysfunction: a systematic review. *Braz J Otorhinolaryngol*. 2022 Sep-Oct;88(5):794–802. http://dx.doi.org/10.1016/j.bjorl.2021.04.001. Epub 2021 Apr 25. PMID: 33965353; PMCID: PMC8068782.
4. Butowt R, Bilinska K, von Bartheld CS. Olfactory dysfunction in COVID-19: new insights into the underlying mechanisms. *Trends Neurosci*. 2023 Jan;46(1):75–90. http://dx.doi.org/10.1016/j.tins.2022.11.003. Epub 2022 Nov 16. PMID: 36470705; PMCID: PMC9666374.
5. Cherobin GB, Guimarães RES, de Paula Gomes MC, Vasconcelos LOG, de Abreu LAN. Intranasal insulin for the treatment of persistent post-COVID-19 olfactory dysfunction. *Otolaryngol Head Neck Surg*. 2023 Sep;169(3):719–724. http://dx.doi.org/10.1002/ohn.352. Epub 2023 Apr 20. PMID: 37078341.
6. Rezaeian A. Effect of intranasal insulin on olfactory recovery in patients with hyposmia: a randomized clinical trial. *Otolaryngol Head Neck Surg*. 2018 Jun;158(6):1134–1139. http://dx.doi.org/10.1177/0194599818764624. Epub 2018 Mar 20. PMID: 29557250.
7. Schöpf V, Kollndorfer K, Pollak M, Mueller CA, Freiherr J. Intranasal insulin influences the olfactory performance of patients with smell loss, dependent on the body mass index: a pilot study. *Rhinology*. 2015 Dec;53(4):371–378. http://dx.doi.org/10.4193/Rhino15.065. PMID: 26275583.
8. Astuti I, Ysrafil. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): an overview of viral structure and host response. *Diabetes Metabol Syndr*. 2020 Jul-Aug;14(4):407–412. http://dx.doi.org/10.1016/j.dsx.2020.04.020. Epub 2020 Apr 18. PMID: 32335367; PMCID: PMC7165108.
9. Shilts MH, Rosas-Salazar C, Strickland BA, et al. Severe COVID-19 is associated with an altered upper respiratory tract microbiome. *Front Cell Infect Microbiol*. 2022 Jan 24;11:781968. http://dx.doi.org/10.3389/fcimb.2021.781968. PMID: 35141167; PMCID: PMC8819187.
10. Jayaprakash NG, Surolia A. Spike protein and the various cell-surface carbohydrates: an interaction study. *ACS Chem Biol*. 2022 Jan 21;17(1):103–117. http://dx.doi.org/10.1021/acschembio.1c00691. Epub 2021 Dec 20. PMID: 34928574.
11. Montazersaheb S, Hosseiniyan Khatibi SM, Hejazi MS, et al. COVID-19 infection: an overview on cytokine storm and related interventions. *Virol J*. 2022 May 26;19(1):92. http://dx.doi.org/10.1186/s12985-022-01814-1. PMID: 35619180; PMCID: PMC9134144.
12. Karamali K, Elliott M, Hopkins C. COVID-19 related olfactory dysfunction. *Curr Opin Otolaryngol Head Neck Surg*. 2022 Feb 1;30(1):19–25. http://dx.doi.org/10.1097/MOO.0000000000000783. PMID: 34889850; PMCID: PMC8711304.
13. Goncalves S, Goldstein BJ. Pathophysiology of olfactory disorders and potential treatment strategies. *Curr Otorhinolaryngol Rep*. 2016 Jun;4(2):115–121. http://dx.doi.org/10.1007/s40136-016-0113-5. PMID: 27529054; PMCID: PMC4982703.
14. Zanza C, Romenskaya T, Manetti AC, et al. Cytokine storm in COVID-19: immunopathogenesis and therapy. *Medicina (Kaunas)*. 2022 Jan 18;58(2):144. http://dx.doi.org/10.3390/medicina58020144. PMID: 35208467; PMCID: PMC8876409.
15. Mukhara D, Oh U, Neigh GN. Neuroinflammation. *Handb Clin Neurol*. 2020;175:235–259. http://dx.doi.org/10.1016/B978-0-444-64123-6.00017-5. PMID: 33008528.
16. Lyman M, Lloyd DG, Ji X, Vizcaychipi MP, Ma D. Neuroinflammation: the role and consequences. *Neurosci Res*. 2014 Feb;79:1–12. http://dx.doi.org/10.1016/j.neures.2013.10.004. Epub 2013 Oct 19. PMID: 24144733.
17. Kaur N, Chugh H, Sakharkar MK, Dhawan U, Chidambaram SB, Chandra R. Neuroinflammation mechanisms and phytotherapeutic intervention: a systematic review. *ACS Chem Neurosci*. 2020 Nov 18;11(22):3707–3731. http://dx.doi.org/10.1021/acschemneuro.0c00427. Epub 2020 Nov 4. PMID: 33146995.
18. DiSabato DJ, Quan N, Godbout JP. Neuroinflammation: the devil is in the details. Suppl 2 *J Neurochem*. 2016 Oct;139(Suppl 2):136–153. http://dx.doi.org/10.1111/jnc.13607. Epub 2016 May 4. PMID: 26990767; PMCID: PMC5025335.
19. Ahmad MA, Kareem O, Khushtar M, et al. Neuroinflammation: a potential risk for dementia. *Int J Mol Sci*. 2022 Jan 6;23(2):616. http://dx.doi.org/10.3390/ijms23020616. PMID: 35054805; PMCID: PMC8775769.
20. Troubat R, Barone P, Leman S, et al. Neuroinflammation and depression: a review. *Eur J Neurosci*. 2021 Jan;53(1):151–171. http://dx.doi.org/10.1111/ejn.14720. Epub 2020 Mar 20. PMID: 32150310.
21. Ousseiran ZH, Fares Y, Chamoun WT. Neurological manifestations of COVID-19: a systematic review and detailed comprehension. *Int J Neurosci*. 2023 Jul;133(7):754–769. http://dx.doi.org/10.1080/00207454.2021.1973000. Epub 2021 Sep 27. PMID: 34433369; PMCID: PMC8506813.
22. Mori K, Nagao H, Yoshihara Y. The olfactory bulb: coding and processing of odor molecule information. *Science*. 1999 Oct 22;286(5440):711–715. http://dx.doi.org/10.1126/science.286.5440.711. PMID: 10531048.
23. LaFever BJ, Imamura F. Effects of nasal inflammation on the olfactory bulb. *J Neuroinflammation*. 2022 Dec 9;19(1):294. http://dx.doi.org/10.1186/s12974-022-02657-x. PMID: 36494744; PMCID: PMC9733073.
24. LaFever BJ, Imamura F. Effects of nasal inflammation on the olfactory bulb. *J Neuroinflammation*. 2022 Dec 9;19(1):294. http://dx.doi.org/10.1186/s12974-022-02657-x. PMID: 36494744; PMCID: PMC9733073.
25. Hummel T, Liu DT, Müller CA, Stuck BA, Welge-Lüssen A, Hähner A. Olfactory dysfunction: etiology, diagnosis, and treatment. *Dtsch Arztebl Int*. 2023 Mar 13;120(9):146–154. http://dx.doi.org/10.3238/arztebl.m2022.0411. PMID: 36647581; PMCID: PMC10198165.
26. Chen M, Reed RR, Lane AP. Acute inflammation regulates neuroregeneration through the NF-κB pathway in olfactory epithelium. *Proc Natl Acad Sci U S A*. 2017 Jul 25;114(30):8089–8094. http://dx.doi.org/10.1073/pnas.1620664114. Epub 2017 Jul 10. PMID: 28696292; PMCID: PMC5544262.
27. Tai AP, Leung MK, Lau BW, Ngai SP, Lau WK. Olfactory dysfunction: a plausible source of COVID-19-induced neuropsychiatric symptoms. *Front Neurosci*. 2023 Mar 20;17:1156914. http://dx.doi.org/10.3389/fnins.2023.1156914. PMID: 37021130; PMCID: PMC10067586.
28. Alarfaj AA, Aldrweesh AK, Aldoughan AF, Alarfaj SM, Alabdulqader FK, Alyahya KA. Olfactory dysfunction following COVID-19 and the potential benefits of olfactory training. *J Clin Med*. 2023 Jul 18;12(14):4761. http://dx.doi.org/10.3390/jcm12144761. PMID: 37510876; PMCID: PMC10381506.
29. Su CY, Menuz K, Carlson JR. Olfactory perception: receptors, cells, and circuits. *Cell*. 2009 Oct 2;139(1):45–59. http://dx.doi.

org/10.1016/j.cell.2009.09.015. PMID: 19804753; PMCID: PMC2765334.
30. Firestein SJ, Margolskee RF, Kinnamon S. Olfaction. In: Siegel GJ, Agranoff BW, Albers RW, et al., eds. *Basic neurochemistry: molecular, cellular and medical aspects*. 6th ed. Philadelphia: Lippincott-Raven; 1999. Available from: https://www.ncbi.nlm.nih.gov/books/NBK28226/.
31. Xydakis MS, Albers MW, Holbrook EH, et al. Post-viral effects of COVID-19 in the olfactory system and their implications. *Lancet Neurol*. 2021 Sep;20(9):753−761. http://dx.doi.org/10.1016/S1474-4422(21)00182-4. Epub 2021 Jul 30. PMID: 34339626; PMCID: PMC8324113.
32. Li X, Lui F. Anosmia, 2023 Jul 3. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2023 Jan. PMID: 29489163.
33. Yu LY, Pei Y. Insulin neuroprotection and the mechanisms. *Chin Med J (Engl)*. 2015 Apr 5;128(7):976−981. http://dx.doi.org/10.4103/0366-6999.154323. PMID: 25836621; PMCID: PMC4834017.
34. Choudhri Y, Maslove DM, Rauh MJ. COVID-19 and the genetics of inflammation. *Crit Care Med*. 2023 Jun 1;51(6):817−825. http://dx.doi.org/10.1097/CCM.0000000000005843. Epub 2023 Mar 20. PMID: 36939259; PMCID: PMC10187540.
35. Pomytkin I, Costa-Nunes JP, Kasatkin V, et al. Insulin receptor in the brain: mechanisms of activation and the role in the CNS pathology and treatment. *CNS Neurosci Ther*. 2018 Sep;24(9):763−774. http://dx.doi.org/10.1111/cns.12866. Epub 2018 Apr 24. PMID: 29691988; PMCID: PMC6489906.
36. Sun Q, Li J, Gao F. New insights into insulin: the anti-inflammatory effect and its clinical relevance. *World J Diabetes*. 2014 Apr 15;5(2):89−96. http://dx.doi.org/10.4239/wjd.v5.i2.89. PMID: 24765237; PMCID: PMC3992527.
37. Brabazon F, Bermudez S, Shaughness M, Khayrullina G, Byrnes KR. The effects of insulin on the inflammatory activity of BV2 microglia. *PLoS One*. 2018 Aug 27;13(8):e0201878. http://dx.doi.org/10.1371/journal.pone.0201878. PMID: 30148836; PMCID: PMC6110462.
38. Li QY, Xu HY, Yang HJ. Effect of proinflammatory factors TNF-α,IL-1β, IL-6 on neuropathic pain. Chinese *Zhongguo Zhongyao Zazhi*. 2017 Oct;42(19):3709−3712. http://dx.doi.org/10.19540/j.cnki.cjcmm.20170907.004. PMID: 29235283.
39. Dadwal S, Heneka MT. Microglia heterogeneity in health and disease. *FEBS Open Bio*. 2023 Nov 9:13735. http://dx.doi.org/10.1002/2211-5463. Epub ahead of print. PMID: 37945346.
40. Spielman LJ, Bahniwal M, Little JP, Walker DG, Klegeris A. Insulin modulates in vitro secretion of cytokines and cytotoxins by human glial cells. *Curr Alzheimer Res*. 2015;12(7):684−693. http://dx.doi.org/10.2174/1567205012666150710104428. PMID: 26159205.
41. Tangvarasittichai S. Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus. *World J Diabetes*. 2015 Apr 15;6(3):456−480. http://dx.doi.org/10.4239/wjd.v6.i3.456. PMID: 25897356; PMCID: PMC4398902.
42. Banks WA, Owen JB, Erickson MA. Insulin in the brain: there and back again. *Pharmacol Ther*. 2012 Oct;136(1):82−93. http://dx.doi.org/10.1016/j.pharmthera.2012.07.006. Epub 2012 Jul 17. PMID: 22820012; PMCID: PMC4134675.
43. Weiss JJ, Attuquayefio TN, White EB, et al, Yale IMPACT Research Team. Tracking smell loss to identify healthcare workers with SARS-CoV-2 infection. *PLoS One*. 2021 Mar 3;16(3):e0248025. http://dx.doi.org/10.1371/journal.pone.0248025. PMID: 33657167; PMCID: PMC7928484.
44. Doty RL. Olfactory dysfunction in COVID-19: pathology and long-term implications for brain health. *Trends Mol Med*. 2022 Sep;28(9):781−794. http://dx.doi.org/10.1016/j.molmed.2022.06.005. Epub 2022 Jun 20. PMID: 35810128; PMCID: PMC9212891.
45. Thakur K, Sagayaraj A, Prasad KC, Gupta A. Olfactory dysfunction in COVID-19 patients: findings from a tertiary rural centre. *Indian J Otolaryngol Head Neck Surg*. 2022 Oct;74(Suppl 2):2840−2846. http://dx.doi.org/10.1007/s12070-021-02364-8. Epub 2021 Jan 18. PMID: 33489853; PMCID: PMC7813170.
46. Ajufo E, Rao S, Navar AM, Pandey A, Ayers CR, Khera A. U.S. population at increased risk of severe illness from COVID-19. *Am J Prev Cardiol*. 2021 Jun;6:100156. http://dx.doi.org/10.1016/j.ajpc.2021.100156. Epub 2021 Feb 13. Erratum in: Am J Prev Cardiol. 2021 Jun;6:100195. PMID: 33615285; PMCID: PMC7880833.
47. Gaddam M, Singh A, Jain N, et al. A comprehensive review of intranasal insulin and its effect on the cognitive function of diabetics. *Cureus*. 2021 Aug 16;13(8):e17219. http://dx.doi.org/10.7759/cureus.17219. PMID: 34540446; PMCID: PMC8442633.
48. Schmid V, Kullmann S, Gfrörer W, et al. Safety of intranasal human insulin: a review. *Diabetes Obes Metabol*. 2018 Jul;20(7):1563−1577. http://dx.doi.org/10.1111/dom.13279. Epub 2018 Apr 6. PMID: 29508509.