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REVIEW PAPER

Anosmia induced by Covid-19: possible mechanisms of its induction and the strategy of stem cells therapy in restoring the sense of smell

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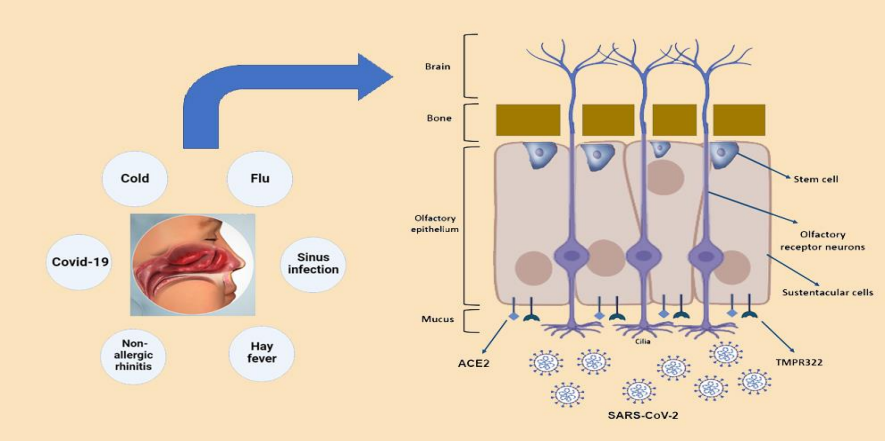
Highlights

- Anosmia can be induced by some viruses, including influenza and Covid-19.
- Anosmia induced by the Covid-19 virus can occur by the mechanism of death of olfactory receptor neurons or damage to the olfactory epithelium.
- Olfactory stem cells can potentially be important for restoring olfactory function.

Graphical Abstract



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Abstract

By determining the quality of food, the sense of smell can play a protective role in humans and determine the suitability of a food for consumption. Sometimes anosmia is presented as a possible disease, and some only present it as a clinical symptom of a specific disease. Anosmia can be caused by the use of drugs, poisons, inflammation, tumor, infection, and some miscellaneous factors. Regarding infection, some viruses, including influenza and Covid-19, can also cause loss of the sense of smell. The chief signs were dry cough, fever, followed by diarrhea, vomiting, and other digestive disorders. According to current evidence, rapid taste or smell loss could also happen as a result of infection with Covid-19. Anosmia refers to the smell inability, and specific anosmia refers to the incapability to recognize a specific smell. Several mechanisms have been proposed for Covid-19-induced anosmia. The possibility of the olfactory receptor neurons death infected with the virus is a plausible mechanism for the loss of the smell sense caused by the Covid-19 infection. Also, another possibility of anosmia is the mechanism of injury caused by the Covid-19 virus to the olfactory epithelium. Olfactory stem cells can potentially be relevant to restore the function of olfactory. The olfactory epithelium has neural stem cells that maintain dynamic neurogenesis throughout life. Understanding the cellular and molecular mechanisms governing these olfactory stem cells is helpful in using them for therapeutic purposes. The aim of this study is to review the anosmia induced by Covid-19 along with the possible mechanisms of its creation and the strategy of stem cell therapy in restoring the sense of smell.

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Introduction

Compared to other animals, humans have lost a large percentage of their sense of smell through evolution. Humans use this sense to determine the quality of the food they want to consume. By determining the quality of food, the smell sense can play a protective role in humans and determine the suitability of a food for consumption. Studies show that people with olfactory disorders are about 50% more likely to eat spoiled food and develop food poisoning (1). It has been found that hyposmia or anosmia may cause the formation of harmful nutritional habits such as high consumption of high-fat and sweet foods in humans (2). Sometimes anosmia is presented as a possible disease, and some only present it as a clinical symptom of a specific disease. However, based on a specific approach, anosmia is classified into seven classes. First, anosmia catarrhalis, which is observed along with a cold, and if it is severe, it can last even after treatment. Second, anosmia ab ozoena is usually seen in people who dissect corpses, flush toilets, etc., who are faced with inhaling bad odors. These people get so used to these smells that they don't understand other smells and finally lose their sense of smell. Third, anosmia a polypo, which is caused by a polyp and is caused through the growth of a polyp in the nose. Enlargement of the polyp causes blockage of the nostrils and blocks the flow of air and pleasant smells. Fourth, anosmia syphilitica, which gradually causes the loss of the olfactory organ. In anosmia verminosa, it creates worms in the nose that cause migraines and sneezing, which eventually causes the smell sense loss. Anosmia a siccitate occurs in fever and inflammatory diseases and causes the smell sense loss. Anosmia paralytica is associated with various types of paralysis and sleep-inducing diseases, which causes compression of the olfactory nerves (3).

Anosmia can be caused by the use of drugs, poisons, inflammation, tumor, infection, and some miscellaneous factors. Painkillers, sedatives, and sleeping pills are medicinal agents that cause the loss of the sense of smell. Alcohol, heavy metals including manganese, cadmium, lead, nickel, and mercury, as well as butyl acetate, benzene, and chloroethylene, are among the toxic substances that cause anosmia. Inflammatory diseases such as multiple sclerosis can also cause anosmia. Tumors such as olfactory nerve tumors, and frontal or temporal brain tumors can too result in loss of sense of smell. Infection with some viruses, including influenza and Covid-19, can also cause loss of the sense of smell (4, 5).

The main symptoms of Covid-19 are dry cough, fever, followed by diarrhea, vomiting, and other digestive disorders. Based on current evidence, rapid loss of smell or taste could also happen as a result of infection with Covid-19 (6). Anosmia refers to the incapability to smell, and specific anosmia refers to the incapability to recognize a specific smell. Specific anosmias indicate the presence of a specific receptor to perceive a specific smell. The terms hyposmia and hyperosmia refer to decreased and increased olfactory ability, respectively, where hyposmia conditions are common but hyperosmic conditions are very rare (7, 8). Several mechanisms have been proposed for Covid-19-induced anosmia. The possibility of the olfactory receptor neurons death infected with the virus is a plausible mechanism for the loss of the smell sense caused by the Covid-19 infection. But this hypothesis is associated with some contradictions (9). The mechanism of the damage of the Covid-19 virus to the olfactory epithelium is determined by the high expression of ACE2 and TMPRSS2 proteins in the supporting cells in the olfactory epithelium (10).

Olfactory stem cells can potentially be relevant to restore olfactory function. The olfactory epithelium has neural stem cells that help dynamic neurogenesis throughout life. Usually, every 30 to 60 days, olfactory sensory neurons change and are substituted by the proliferation and differentiation of some immature progenitors and multipotent progenitor cells (11). Understanding the cellular and molecular mechanisms governing these olfactory stem cells is helpful in using them for therapeutic purposes (12). Knowing the genes involved in disease is very important. However, anosmia is not well characterized genetically. Genes involved in some syndromic cases have sometimes been identified (13). It has been observed that an uncommon mutation in the TENM1 gene can be associated with anosmia, and hyposmia was observed in a mouse model lacking the Tenm1 gene (14). The aim of this study is to review the anosmia induced by Covid-19 along with the possible mechanisms of its creation and the strategy of stem cell therapy in restoring the sense of smell.

Olfactory disorders and etiology of olfactory loss

Anosmia refers to the incapability to smell, and specific anosmia refers to the incapability to recognize a specific smell. Specific anosmia indicates the presence of a specific receptor to perceive a specific smell. Several factors can cause anosmia (Figure 1). The terms hyposmia and hyperosmia refer to a decrease and an increase in olfactory ability, respectively, where hyposmic conditions are common but hyperosmic conditions are very rare (7, 8). The term phantosmia refers to the perception of odors in the absence of an associated odor source, and the term parosmia refers to the qualitatively "false" perception of odors. For example, after smelling a rose, a person perceives something other than the common smell of roses. Parosemia is often associated with reduced olfactory sensitivity, and this problem can occur after craniocerebral trauma or after viral infections of the upper respiratory tract (7, 15).

The main causes of olfactory disorders include nasal problems, trauma, age-related olfactory disorders, or neurological disorders including Alzheimer's disease or Parkinson's disease (16, 17). The term "normosmia" refers to the normal function of smell and it changes physiologically with age. The human ability to detect smells improves throughout life and reaches its maximum in the fourth decade and decreases sharply after the sixth decade. Olfactory disorders are associated with various diseases including neurological disorders, traumatic brain injuries, sinus diseases, and post-infection disorders. So far, the etiology of olfactory loss has not been fully explained (18, 19). Four different reasons have been proposed to explain the olfactory disorders in patients with SARS-CoV-2 infection, which include virus penetration into the brain and effect on olfactory centers, loss of olfactory receptor neurons, nasal congestion and rhinorrhea, and damage to supporting cells in the olfactory epithelium (20).

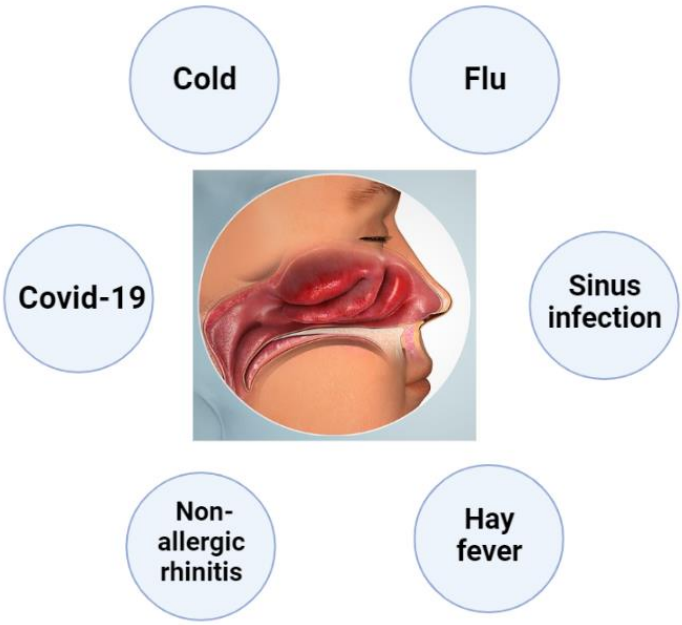

Figure 1. Some common causes of anosmia. Cold, flu, sinus infection, hay fever, non-allergic rhinitis and Covid-19 are the common reasons of anosmia.

Clinical symptoms of Covid-19 with focus on symptoms related to CNS and PNS

The key signs were dry cough, fever, followed by diarrhea, vomiting and other digestive disorders. Based on current evidence, rapid loss of smell or taste could also happen as a result of infection with Covid-19 (6). In relation to Covid-19, several central nervous system (CNS)-related symptoms have been observed, including acute cerebrovascular disease, epilepsy, impaired consciousness, dizziness, headache, ataxia, and viral encephalitis (6). Elderly people with a history of chronic diseases are at risk of delirium and consciousness in the face of acute infections. These people are also highly susceptible to Covid-19 and may experience complications such as confusion and encephalopathy. In addition, people with viral infections such as Covid-19

may also develop coronary artery disease. This problem may be caused by a disorder in the coagulation system. Clot formation is present in some critical patients with COVID-19 (21, 22).

Symptoms and signs of Covid-19 associated with the peripheral nervous system (PNS) are less severe and include Guillain-Barré syndrome and muscle pain, and hyposmia/anosmia. The two complications of anosmia and aging are the most usual manifestations related to PNS in Covid-19 viral infection, which have also been observed in former coronaviruses. Usually, these signs come on rapidly with less olfactory signs including excessive nasal discharge and nasal congestion. Anosmia and aging are more common in asymptomatic individuals (23). Therefore, people with these signs might be probable carriers of the virus and contribute to the transmission of the virus. Most patients with Covid-19 gradually regain their smell sense and taste after passing the course of the disease. This virus can be transmitted to the brain via the pathways of olfactory and disrupt the integrity of the neuroepithelium of olfactory via ACE2 and TMPRSS2 receptors in host cells (24). This disorder in the neuroepithelium of olfactory results in anosmia. However, some researchers have stated that anosmia occurs because of inflammation in the nerves of olfactory and not due to damage to the receptors structure (25).

Pathway of Covid-19 from the nose to the brain

Following viral infection of humans and some animal models with Covid-19, this virus exists in the cerebrospinal fluid and brain parenchyma, but how the virus gets there is still unclear (26). The probable routes comprise three key access routes to spaces containing cerebrospinal fluid; vascular/systemic, mediated by crossing of leukocytes from the blood-brain barrier or endothelial cells; Nervous, moving along the cranial nerves (nervus terminalis, vagus, glossopharyngeal, olfactory, facial, trigeminal); or a combination of these three paths. Researchers hypothesize that the Covid-19 virus infects the brain through the olfactory pathway. The olfactory and terminal neurons are valid ways to reach the brain (27).

The possibility of death of olfactory receptor neurons infected with the virus

The possibility of the death of olfactory receptor neurons infected with the virus is a plausible mechanism for the loss of the smell sense caused by the SARS-CoV-2 infection. Nevertheless, three main contradictions exist in this scenario, including the absence of virus in the relevant neurons, the absence of protein expression of virus, and the time course of cellular regeneration versus clinical improvement (9). Replacement of olfactory receptor neurons after their death requires eight to ten days, as well as about five additional days for cilia to mature, but the period of recovery of olfactory sensation in Covid-19 viral infection is often less than a week. Therefore, neuron replacement often takes longer than the usual olfactory recovery time after anosmia. Also, by examining the expression of virus entry proteins, it has been predicted that developed olfactory receptor neurons do not produce ACE2 receptor and therefore it is possible that these cells are not infected by the Covid-19 virus (28). Researchers believe that expression of ACE2 receptors, TMPRSS2, and viral entry proteins in mature olfactory neurons are absent. Taken together, these data do not seem to support that many cases of Covid-19-induced anosmia result from direct damage to olfactory receptor neurons by the virus attack. However, in prolonged cases of anosmia, olfactory neurons death is likely (29).

SARS-CoV-2 damage to supporting cells in the olfactory epithelium

The mechanism of the damage of the Covid-19 virus to the olfactory epithelium is determined by the high expression of TMPRSS2 and ACE2 receptors (proteins required for the virus to enter the host cell) in the supporting cells in the olfactory epithelium. Data from RNAseq indicated that only one to three percent of host cells express ACE2, whereas immunocytochemistry revealed that the vast majority and perhaps all host cells contain the ACE2 receptor (10). One of the reasons that can justify this discrepancy is the inability of the RNAseq technique to quantify and determine the amount of protein expression. Research has shown that the cilia of neurons may temporarily loss of expression of protein, meaning temporary dysfunction of neuron (30).

The rate of death and regeneration of supporting cells is much higher than the rate of death and regeneration of olfactory neurons, which must mature and develop their dendrites and axons. Therefore, the rapid remodeling of supporting cells is consistent with the fast recovery of olfactory sensation observed clinically in most cases (31, 32).

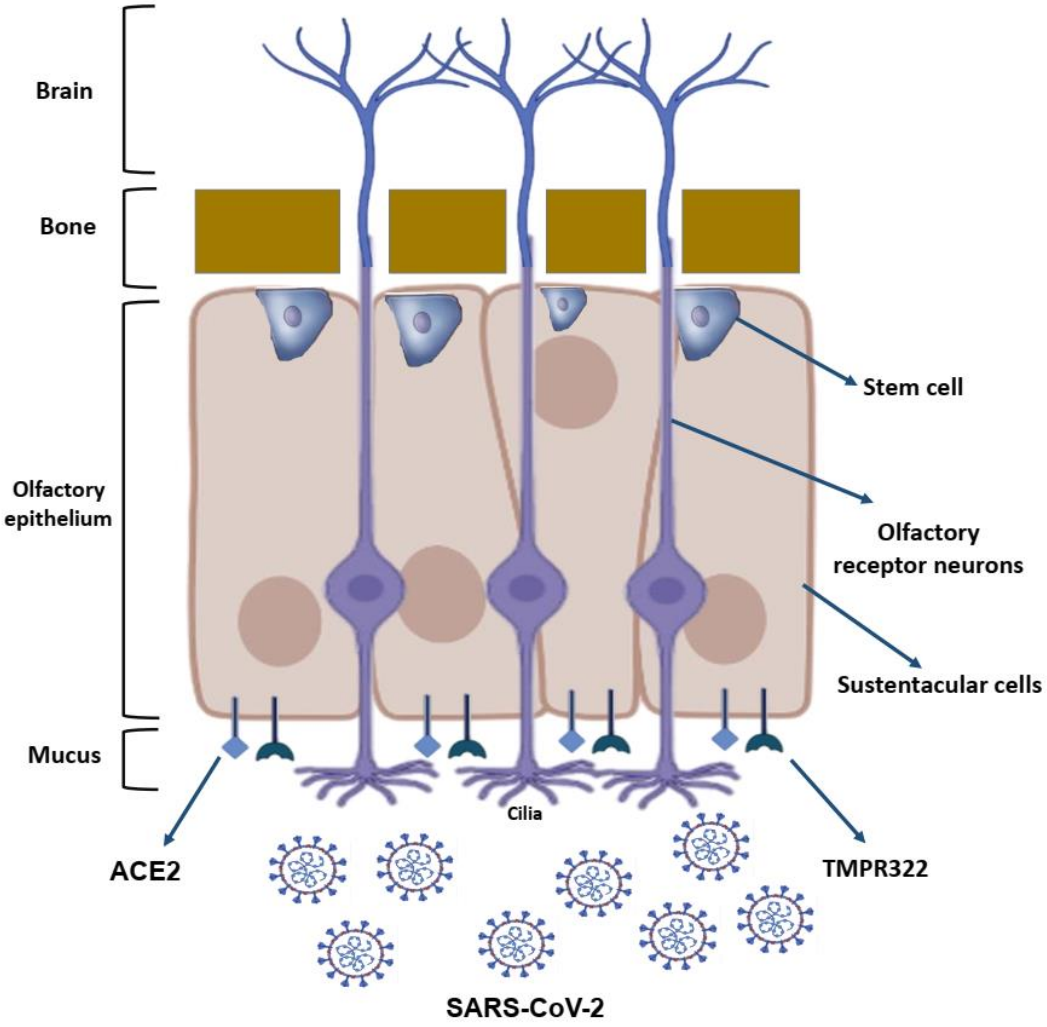

Figure 2. Entrance of Covid-19 virus to the olfactory epithelium. ACE2 and TMPRSS2 receptors are present on the surface of sustentacular cells. Destruction of these cells has a negative effect on olfactory receptor neurons and causes damage to the sense of smell.

Potential of olfactory stem cells to restore olfactory function

Neural stem cells are exist in the olfactory epithelium that support active neurogenesis throughout life. Usually, every 30 to 60 days, olfactory sensory neurons change and are substituted by the proliferation and differentiation of some immature progenitors and multipotent progenitor cells (11). After birth, two types of multipotent progenitor cells including globose basal cells and horizontal basal cells are observed in the olfactory epithelium. Globose basal cells are mitotically active and can replace sensory neurons and other kinds of cell in the olfactory epithelium. But horizontal basal cells are very stable. Following damage to mature cells in the olfactory epithelium, horizontal basal cells are induced to proliferate and differentiate into globose basal cells and all types of olfactory cells (33). Horizontal basal cells can be considered a source of reserve stem cells that rarely divide under normal conditions, and it is possible for them to generate a pool of active globose basal cells (34). Horizontal basal cells proliferate more rapidly in response to injury and can regenerate cellular components of the sensory epithelium. Therefore, olfactory progenitor cells can be considered as a promising therapeutic solution to replace epithelium cells with the aim of restoring olfactory function (35). It should be

noted that the number of proliferating olfactory progenitors decreases gradually with age (36). One strategy to restoring olfactory sensory function could involve activating resident horizontal basal cells in situ to differentiate into globose basal cell progenitors (37). Understanding the cellular and molecular mechanisms governing these olfactory stem cells is helpful in using them for therapeutic purposes (12).

The genetics behind the loss of smell

Knowing the genes involved in a disease is very important. Some hereditary sensory defects, including congenital hearing loss and blindness, have been well studied from a genetic point of view, and this information can be a good way to use gene therapy and cell therapy to solve these disorders (38). Mutations and disruptions in more than 90 different genes can be associated with hereditary hearing loss disorder, and with the help of gene therapy approaches, hearing loss has been successfully treated in mice (39). In the case of congenital blindness, gene therapy can be an attractive target because there is relative access to the retina from outside the body. Familial retinal degeneration can be associated with mutations and disruptions in more than 200 genes that are involved in the death of photoreceptor cells, and gene therapy approaches with gene transfer by viral vectors for many diseases characterized by hereditary blindness, in it has been going on for the last decade (40). However, anosmia is not well characterized genetically. Genes involved in some syndromic cases have sometimes been identified (13). It has been observed that an uncommon mutation in the TENM1 gene can be related to anosmia, and in a mouse model lacking the Tenm1 gene, it was observed that hyposmia occur (14). Over than 200 genes have been found to be involved in patients with congenital visual impairment and over than 100 changed genes in cases with congenital hearing impairment (41).

Conclusion

The disease of Covid-19 is associated with some symptoms such as dry cough, fever followed by diarrhea, vomiting and other digestive disease. But olfactory dysfunction can influence the affected person for a long time as a complication of this disease. The olfactory dysfunction induced by Covid-19 can be explained by different mechanisms. Following viral infection of humans and some animal models with SARS-CoV-2, this virus exists in the cerebrospinal fluid and brain parenchyma, but how the virus gets there is still unclear. The possibility of the death of olfactory receptor neurons infected with the virus is a plausible mechanism for the loss of the smell sense caused by the Covid-19 infection. Nevertheless, there are three major contradictions in this scenario, including the absence of virus in the relevant neurons, the absence of the viral protein expression, and the time period of cellular regeneration vs. clinical improvement. The mechanism of the damage of the Covid-19 virus to the olfactory epithelium is determined by the high expression of TMPRSS2 and ACE2 receptors in the supporting cells in the olfactory epithelium. A detailed understanding of the mechanisms of anosmia induced by the Covid-19 virus requires further studies. Two types of multipotent progenitor cells including globose basal cells and horizontal basal cells are observed in the olfactory epithelium. Globose basal cells are mitotically active and can replace sensory neurons and other kinds of cell in the olfactory epithelium. But horizontal basal cells are very stable. Horizontal basal cells proliferate more rapidly in response to injury and can regenerate cellular components of the sensory epithelium. Therefore, olfactory progenitor cells can be considered a promising therapeutic solution to replace epithelium cells with the aim of restoring olfactory function. Understanding the cellular and molecular mechanisms governing olfactory stem cells is helpful in using them for therapeutic purposes.

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