REVIEW ARTICLE

Biochemical and Other Mechanisms Associated With Olfaction and Taste Abnormalities in Covid-19

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ABSTRACT

Coronavirus (SARS-CoV-2) spreads from its initial nasal reservoir to produce respiratory problems and neurological manifestations. Viral spike protein-S binds with host receptor angiotensin-converting enzyme 2 with the assistance of membrane fusion protease. Average smell and taste disorders prevalence was 18.8% and 14.1% respectively.

The objective of this narrative retrospective study was to explore mechanisms underlying olfactory and gustatory manifestations. For obtaining novel information, we selected articles from January 2021 to January 2023. We searched terms like neurological manifestations, anosmia, loss of taste in COVID-19, and SARS-CoV-2 as keywords using PubMed. After scrutiny, we excluded articles with accessory and non-relevant information and finally selected 23 articles.

Various immune mechanisms like cytokine storm and direct neuroinvasions result in neurological manifestations. Role of various micro RNAs in molecular pathology point towards future research to explore epigenetic neuropathological mechanisms to help in designing novel therapeutic remedies. Global awareness and vaccination protocols had greatly reduced occurrence of disease.

Key Words: Ageusia, anosmia, biochemical, COVID-19, mechanisms

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INTRODUCTION

A new strain of SARS-CoV-2 was isolated in China at the end of December 2019 resulting in serious pneumonia[1]. The World Health Organization declared it as a pandemic in March 2020. In a highly alarming report, the American Association for Cancer Research and COVID-19 announced that by January 2022, =289 million subjects were identified globally to have COVID-19 and =5.4 million had expired from the disease[2]. The higher genomic size gives more possibilities of flexibility resulting in recombinations and mutations favoring genetic diversity and spread of corona virus to other species[3].

The method of SARS-CoV-2 entry in the target cells is membrane fusion or endosomal pathway. This occurs once the spike (S) protein of virus binds with the receptor angiotensin-converting enzyme 2 (ACE2) located in the lungs, liver, blood vessels, nervous system, and other places with the assistance of membrane fusion protease (TMPRSS)[4].

COVID-19 presented with multiple stages of severity. It could be asymptomatic or may commence with upper respiratory tract symptoms like pyrexia, myalgia, tiredness, sneezing, nasal secretions, and irritation in throat. When it progressed to moderate stage, cough and fever due to pneumonia occurred with or without hypoxemic spells. At this stage, chest radiography mainly CT scans showed the lesions. In severe stage, there was pneumonia with hypoxemia (SpO2 <92%). These were followed by highly serious states like acute respiratory distress, cardiac injury or failure and shock; and could be accompanied by acute renal injury, encephalopathy and clotting problems. Such cases required an emergency intensive care unit admission[4].

It is in the moderate to severe stage of the disease that the CNS injury occurs as pronounced feature[5]. The prevalence of anosmia was 49%. In different studies, about 60 days post COVID-19, the average prevalence of anosmia and loss of taste was 18.8% and 14.1%

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respectively in 2021. The taste variations were ageusia and hypoguesia. The average anosmia duration was about 10 days in mild disease, which settled completely in about 89% cases in four weeks[6]. Some 5% of cases showed a prolonged course or no improvement[7]. There could be a combined loss of smell and taste.

The other lesions coexisting with dysgeusia were tongue and palatal ulcers, gingivitis, halitosis, fissures in tongue, hyperplasia of papillae, candidiasis, dry mouth, and lingual plaques. These symptoms could be attributed to lower immune system and simultaneous antibiotic usage[8].

This review contains general information about the causative virus and COVID-19 disease itself followed by the general information about the mechanisms for smell and taste manifestations. This review in particular highlights the said mechanisms in COVID-19 for gaining guidelines for the future researchers to explore the treatment strategies for these cases.

General Background of Mechanisms in Neurological Complications:

The initiators of infectivity existed on both sides i.e. virus and host cell (viral spike protein variations and host cell surface proteins, mainly ACE2 and TMPRSS2)[9].

There are four types of viral structural proteins called Spike (S), Envelope (E), Membrane (M) and Nucleocapsid (N) proteins.

The RNA genome lies in N protein where as S, E and M collectively form viral envelope. S1 and S2 are type-1 membrane glycoproteins. S1 helps in attachment of virus and S2 works for its fusion with host cell membrane. On the host cell, ACE2 has affinity for S proteins. This is followed by host serene proteases called TMPRSS2, TMPRSS4, furin, endothelial cathepsins helping in membrane fusion by protein catalysis and viral entrance in target cells[10]. The viral inhabitance and infectivity is determined by the Receptor Binding Domain (RBD) of the subunit S1 viral spike protein that attaches by increased affinity to the peptidase domain of ACE2. The genetic mutations at RBD determine variations of infectivity between various regions of the world. The variations outside RBD like single nucleotide polymorphism G614 results in generation of dominant viral strain in the pandemic and need further research[9]. After the entrance of the viral genome in cell, it replicates its polyproteins 1a and 1ab tagged with genes pertaining to open reading frame called ORF-1a and ORF-1b. These mechanisms take over the control of target cell ribosomal functions[11]. The host cell apoptosis occurs by ORF3a, ORF3b, ORF6 and ORF7a. The expression of cytokines is increased by viral ORF7a. Host cell interferon production is inhibited by ORF6, host cell autophagy by mitochondrial dysfunction due to ORF9b effects. The effects such as activation of inflammasome complex, release of interleukin-1 beta, stress response of endoplasmic reticulum, malfunction of lysosomes, caspase-independent cell necrosis is produced by ORF8b[12].

The viral invasion of nervous tissue by inflammatory state caused by cytokines produced neurological manifestations[13]. T cell infiltration also had role in neuroinflammation in about 70% of subjects, which showed $CD8^+$ T-cell infiltration. The infiltration of neutrophils, T-cells with the activated microglial cells producing microgliosis were also found in brain autopsies of such cases[14]. The immune system autoantibodies, molecular, cellular and biochemical mechanisms were noted in various neurological complications[15]. Apart from olfaction and gustation, the other neurological manifestations were also found such as stroke, neuropathy, damage to choroid plexus, blood brain barrier damage, direct cranial nerve damage, gene regulation problems, glial cell damage, and audio-vestibular problems. These problems had various underlying mechanisms which are not addressed in this review.

The severity of disease was related to complement mainly C3, C5a and C5b, their hyper activation caused clotting, formation of thrombi and damage to endothelial cells[13]. The interleukins (IL6, IL8, IL17A), TNF-α, activated perivascular astrocytes, and the endothelial cells were found implicated in the cytokine storm. The immune process damaged the endothelium. This was shown by raised levels of D-dimers, soluble vascular cell adhesion molecules, plasma fibrinogen, thrombomodulin, von Willebrand factor, TNF receptor 1, haparan sulphate, alpha-2 antiplasmin and plasminogen activator inhibitor[16,17].

Mechanism by retrograde axonal transport of virus:

The virus can travel through trigeminal, olfactory, facial, glossopharyngeal, and vagus nerves to infect parts of the brain[18]. The autopsies from frontal lobe and cerebellar cortex, trigeminal ganglion, olfactory bulb, medulla oblongata, and olfactory nerves showed presence of SARS-CoV-2[19]. The inoculation of SARS-CoV-2 in olfactory epithelium of mice revealed entry of virus in the cerebral cortex and hippocampus, and in other experiments, the viral antigen was detected in the neuroglial and nerve cells[20].

METHODOLOGY

In this retrospective narrative review, the mechanisms underlying neurological manifestations related to COVID-19 subjects were analyzed. As less work was done in the initial periods of COVID-19 due to a lack of in-depth research aimed to explore the underlying mechanisms, therefore we targeted the articles that were published in the most recent years. For this purpose, the related articles were searched from January 2021 to January 2023. We utilized PubMed for this task.

The methods utilized to seek these articles were carried by using group of search items. First by putting the term COVID-19 followed by the type of neurological complication and mechanism like COVID-19 anosmia mechanisms, COVID-19 biomarkers in neurological complications, COVID-19 biomarkers in olfactory complications, and COVID-19 dysgeusia mechanisms. Most of these articles included comprehensive reviews, original research manuscripts, and case studies. The articles indicating six months post COVID period and thereafter for the presence of neurological complications, were included in this review.

In each search output, we sorted out the underlying molecular mechanisms also. We also looked at the references of all the articles found and tried to get the related molecular mechanisms. Further, the bibliographies of related articles were assessed to observe and search the pertinent literature. More emphasis was given to articles published in year 2022 so that latest information could be obtained. After getting all the pertinent information, we set the concluding remarks in discussion section to get further research track for future workers. The inclusion criteria were year of publication, relevance with the title, and aim of related article. The exclusion criterion was accessory and non-relevant information.

After scrutiny and exclusion, the total number of articles selected was 23. We found 16 articles related to anosmia and altered sense of olfaction and seven articles for gustatory deficits. For each major deficit, we explored the related mechanism underlying it in these published papers.

SPECIFIC MECHANISMS AT VARIOUS LEVELS ALONG THE OLFACTORY PATH

From the site of olfactory epithelium up to the olfactory cortex

(i) Mechanisms at the Level of Olfactory Epithelium:

The infection starts at the nasal passage where the narrow olfactory cleft could be occluded by congestion and mucus to produce conduction block for smell. This mechanism was not operable because some cases showed anosmia before nasal symptoms and its recovery before olfactory cells's regeneration. Normally, the olfactory stem cells regenerate to produce the olfactory sensory cells and the sustentacular (supporting) cells. The SARS-CoV-2 mainly infects the supporting cells and the stem cells to express ACE2[21]. During supporting cell's regeneration in about eight days, the olfactory cell dendrites mature producing recovery of smell[9].

Molecular mechanisms involving *expression of ACE2 and trans-membrane serine protease 2 (TMPRSS2) in the supporting cells* was found as the main cause of anosmia[22]. The viral protein Nsp13 binds with ciliary centrosomes to produce ciliary damage and anosmia[23] (Table 1). The ACE gene has many genetic variations producing delta and omicron strains. Serene protease inhibitors like camostat mesylate and nafamostat mesylate could help treating anosmia and also reduce viral infection (Table 1)[22,24]. Some authors have indicated that TMPRSS2 expression occurs in scanty amounts in the olfactory cells[25].

(ii) Variation in Enzymatic Metabolism of Sustentacular Cells:

The sustentacular cells normally produce soluble proteins which mix with secretions of olfactory glands so that the receptor cells of sensory neurons can detect the sense of olfaction. When the sustentacular cells get infected with the virus, the function of enzymatic metabolism gets disturbed. These effects produce degradation of odorant molecules resulting in decreased sense of smell (Table 1)[26].

(iii) Mechanisms Based on the Effects of Cytokine Storm on Sustentacular Cells:

The cytokines are released at the olfactory epithelial ACE2 receptors like interleukin-6, IL 1β[6]. After the virus binds with toll-like receptors, the IL 1β is released which is cleaved by caspase-1 leading to activation of inflammosomes, apoptosis through TNF-α or neuropilin to produce anosmia[27]. After three months of post-COVID Syndrome (PCS), the low-grade inflammation, high neutrophil count, pro-inflammatory response, and decreased local immunity could prolong anosmia[28].

(iv) Effect on Stem Cell Regeneration:

Due to inflammation and apoptosis of the stem cells because of complementing factors, neutrophils, and cytotoxic cells around them, a prolonged span of anosmia can occur (Table 1)[6].

(v) Mechanism by Direct Effects on the Sensory Neurons:

The sensory cells showed replication of viral genes, non-structural protein genes such as nsp14 and RNA-dependent RNA-polymerase genes like RdRp in real time. Some therapeutic target genes viz. chemosensory modulator bromodomain-containing protein 2 (BRD2) and early-growth response gene (EGR1) manifested higher expression in human peripheral neurons following COVID-19[29]. Expression of immature class III β-tubulin and mature olfactory membrane protein in the olfactory epithelium was also noted (Table 1). Autopsy examination of 19 cases of such infection carried out for sensory neuron membrane proteins showed positive results[30]. The olfactory sensory neurons gave reduced receptor gene expression of adenylyl cyclase 3 and other key olfactory transcripts that caused hyposmia (Table 1)[31]. However, some asthmatics were protected due to respiratory allergen exposure causing less ACE2 expression in upper air passages[32].

(vi) Damage to Olfactory Bulb:

The olfactory bulb neurons are regarded as 2nd order neurons in the olfaction pathway. In COVID-19 cases, it showed an abnormal enhancement on magnetic resonance images. A mechanism in the form of upstream movement of virus through the cribriform plate towards olfactory bulb and from here to other parts of brain was also proposed (Table 1)[33]. The human olfactory bulb autopsies also revealed the presence of virus in peripheral neurons[30].

(vii) Mechanism of Viral Spread to Hypothalamus **by** *Nervus Terminalis (XIII Cranial Nerve)*:

This nerve is a microscopic plexus of unmyelinated nerves projecting to olfactory trigone by passing under the medial olfactory gyrus. It was proposed that the expression of ACE2, cathepsin B, and cathepsin L in this nerve, causes facilitation of viral transmission through it to nearby brain structures. At the lamina terminalis, this nerve facilitates entry of virus to preoptic area and hypothalamic arcuate nucleus to disturb the pituitary hormone secretion, thermoregulation, and autonomic responses[34].

Mechanisms Involved in Gustatory Dysfunctions

(i) Direct Effect on Gustatory Receptor Cells:

There was a direct mode of infection of gustatory receptor cells due to ACE2 and TEMPRSS2 as compared to olfactory, where it was an indirect effect coming from the infection of the supporting cells (Table 2)[35]. This was reported in harvested circumvallate papillae immune staining experiments on Sprague-Dawley rat cells, which showed ACE2 expression causing decrease in bud cells and taste bud numbers supporting ageusia[36]. Different types of tastes (salt, sweet, bitter, sour, and umami) had variable mechanisms supported by some authors and not favored by others[37,38].

(ii) Mechanisms based on the effects of Cytokine storm

This was explained in Table 1.

(iii) Effect on Non-gustatory Cells of Tongue:

A different type of taste sensation called chemesthesis (feeling of coldness after eating mint or heat from chilies) was decreased. This was due to inflammatory effects on non-gustatory cells, which are normally involved in transmitting general sensations. This had a separate trigeminal general sensory path, as it does not start from taste buds, mechanism was unknown or may be due to cytokines, all the three senses (olfaction, taste and chemesthesis) may be affected simultaneously[39].

(iv) Effect on Salivary Glands:

The glandular epithelium of the salivary glands express ACE2. The subsequent damage to this epithelium causes reduction in saliva and dry mouth due to ACE2 effects resulting in decreased sense of taste.

(v) Effect of SARS-CoV-2 on Nerves Carrying Taste Sensation:

The branches of facial, glossopharyngeal, and vagus nerves carry taste sensations. These fibers along their path also join other nerves such as branches of the trigeminal nerve. The direct damage to these cranial nerves by the viral pathology were also considered as an important cause to produce gustatory manifestations (Table 2)[8].

(vi) Mechanism of Furin Expression:

The furin is a cytoplasmic enzyme involved in the priming of the virus. The expression of furin was noted in the fungiform papillae, neural tissue, and salivary glands (Table 2)[40].

(vii) Mechanism Indicating Effects on Zinc Chelation:

The inflammatory effects of viral infection on the taste buds can result in zinc environment alteration[8,41]. Conduction of taste in nerves and gustatory perception is based on the role of zinc, which acts as cofactor for alkaline phosphatase to maintain taste[42]. Zinc dependent enzyme (Gustine) is influenced by carbonic anhydrase

Table 1. Main Mechanisms Involved in Olfactory Manifestations with Their Therapeutic Aspects

Anosmia and Hyposmia	**Mechanisms**	**Therapeutic Comments**
	-Expression of ACE2 and TMPRSS2 in the supporting cells	-Camostat mesylate and Nafamostat mesy late to reduce infectivity
	-Polymorphism of ACE2 and TMPRSS2 genes and/or variations of viral S-protein	-**
	-Nasal enzymes metabolic genetic variation for odorants by supporting cells	-Enzymatic inhibitors need to be explored**
	-Cytokine storm (TNF-α, IL-1β and IL-6 levels) causing apoptosis	-Cortisone in early and late stages with care about their side effects
	-Expression of non-structural protein gene (nsp14)	-Inhibitors**
	-Expression of RNA-dependent RNA-polymerase (RdRp) gene	-Remdesivir, other Inhibitors**
	-Viral protein Nsp13 binding to ciliary centrosomes	-**
	-Inflammation and apoptosis of stem cells by complement factors, neutrophils and cytotoxic cells around them	-Eculizumab to decrease inflammation
	-Neuronal genes overexpression (Bromodomain-containing protein 2 (BRD2)	-BRD2 inhibitors still in clinical trial, **
	-Early-growth response gene (EGR1), has role in infection and inflammation	-**
	-Immature class III β-tubulin expressed by olfactory neuronswhich, upon infection are phagocytosed by macrophages	-Colchicine / others are under trial but**
	-Under expression of adenylyl cyclase 3 (Neuronal receptor gene)	-Endosome inhibitors chloroquine, azithromycin showed limited efficacy**
	-Olfactory bulb (second order) neuronal inflammatory damage	-** Cortisone with precautionary measures.

Legend: **Needs further research

Table 2. Main Mechanisms Involved in Gustatory Manifestations with Their Therapeutic Aspects

Ageusia and Dygeusia	**Mechanisms**	**Therapeutic Comments**
	-Direct effect on gustatory receptor cells (expression of ACE2 and TMPRSS2) resulting in damage and improper differentiation	-Protease inhibitors, Corticoids
	-Similar mechanism on salivary gland's ACE2 receptors resulting in dry mouth	-Protease inhibitors
	-Cytokine storm	-Cortisone in early and late stages with care about their side effects
	-ACE2 mediated damage of cranial nerves VII, IX and X resulting in taste problem	-Corticoids, antivirals
	-Furin expression (proteolytic enzyme) by fungiform papillae with role in priming of virus	-**
	-Zinc chelation by taste bud inflammation	-Zinc therapy
	-Gustatory center's viral infiltration	-**
	-Polymorphism of uridine diphosphate (UDP) glycosyltransferase genes causes hypogeusia	-**

Legend: **Needs further research

for production of taste buds. Oral zinc stimulates the food intake by its effect on the hypothalamus with its role in taste disorders therapy. The zinc deficiency causes taste problems (Table 2)[35].

(viii) Direct Infiltration of Virus on Neurons in Taste Centers:

Like direct effects of SARS-CoV-2 on olfactory center, the centers for taste perception can also be affected directly. This can be based on factors which produce neuropathy[42].

(ix). Genetic Mechanisms:

The *polymorphism in uridine diphosphate (UDP) glycosyltransferase family of gene loci* with a role to eliminate toxic products was noted mainly UGT2A1 and UGTA2 genes as factors for ageusia and anosmia (Table 2)[43].

DISCUSSION

The mechanisms underlying neurological manifestations in COVID-19 are multifaceted. The direct infection of the virus on peripheral sensory neurons happened through the entry component ACE2. This is followed by the events involved in the lifecycle of virus ahead like the molecular mechanisms. The genes associated with chemosensory functions get changed and undergo expression by the viral infection. The pattern of gene expression needs further exploration to understand the basic background to design appropriate therapeutic remedies against such infections.

COVID-19 is characterized by predominance of the pulmonary as opposed to neurological signs that are lesser. Since the neurological signs can occur during the active phase as well as long afterwards in the post COVID-19 phase with unfavorable consequences and morbidity so they should never be ignored and must be diagnosed and remedied early.

A regional variation was also noted related to COVID-19. Researchers have found the main reason for lower prevalence in Asia as compared to the West, which could be due to a genetic variation either in the viral spike proteins (S-protein) or host cell surface proteins. There can be genetic polymorphism at the level of ACE2 or at transmembrane serine protease 2 (TMPRSS2) (Table 1). It is found that different populations have variations in degree of the individual complications, for instance, anosmia variations occurred due to dissimilarities in S proteins of the viral genealogic lineage at one hand and dissimilar host proteins on the other end. This will certainly modify the entrance of virus and overall level of infectivity[9].

Although various mechanisms were pointed by different workers to produce anosmia but the overall findings for it gave importance to the damaged sustentacular cells than the olfactory receptor cells. Viral spread from sustentacular cells through cribriform plate into nearby cerebrospinal spaces and from there to adjacent brain regions, is accepted as final mechanism till date[44]. This does not ignore the effects due to olfactory sensory neurons totally as some workers found damage of cilia of these neurons and presence of viral particles in neurons. In addition, the other supplementary effects like the radiological evidence of damage to olfactory bulb and reduction in size of the olfactory cortical area cannot be ignored because these structures form part of the olfactory path.

The experimental evidence of expression of ACE2 in oral mucosal cells and cell membranes of taste buds can easily explain the direct damage occurring at taste receptor cells as well as secondary pathogenesis of inflammation due to cytokines at mainly local and systemic levels to induce hypogeusia, dysgeusia, or ageusia. Various consequences of SARS-CoV-2 infection in oral region in the mucosa itself and gingiva with problems in taste sensations need further research to approve a relation among these stated lesions and disease. Exploration of the nature of these lesions for being a kind of primary manifestation of the disease versus the possibilities operating due to secondary effects is mandatory.

One cannot ignore the secondary effects on taste; like use of medications, decreased immune system mechanisms, reduction in local blood supply, inflammatory effects at both local and systemic levels, and abandoned personal oral health care. The secondary effects due to reduced salivary secretion (dryness of mouth) and direct effects on nerves involved in the path of taste sensation were also noted. The treatments for taste disorders are currently taken as arbitrary as they still need further research workup. The ageusia and anosmia has long duration effects like perceptivity about food, dietary practice of the individual and the way one communicates at societal or social level.

The parameters of the quality of life are affected negatively by the neurological complications in the form of smoke inhalation and consumption of spoiled food in case of olfactory dysfunction. This can cause decrease in appetite and lacking interest in eating one's own favorite foods, malnutrition, and decreased social life. Such effects point to the need for further research and explore treatment remedies against these complications.

This emphasizes the need to diagnose the problems meticulously. Hence, an essential earlier screening, diagnosis at clinical as well as laboratory levels for assessment of these problems, followed by their effective management, is mandatory.

CONCLUSION

This review had enumerated proteins, enzymes related to SARS-CoV-2 entrance, various receptors and mechanisms. The sequelae of cytokine related pathogenesis, immune mechanisms and direct

neuroinvasion result in neurological complications. It was necessary to explore the molecular mechanisms operating in SARS-CoV-2 infection, define research gaps to direct further research to predict the diagnosis, identify the patient stratifications, timely target the preventive steps, to arrange medical services, to design appropriate treatment strategies, and seek an improved prognostic assessment. The role of various micro RNAs in the molecular pathology of inflammatory process point towards future research targeted to explore the epigenetic mechanisms to help in designing the new treatment modalities. The incidence of this disease was reduced by the extensive measures taken globally such as surveillance, isolation, and data about contacts, discouraging public movements, social distancing, frequent hand washing, increased awareness, and most importantly, the vaccination protocols.

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Authors' Contribution: LVU and QJ made substantial contributions to the conception, design of the work, the acquisition, analysis, interpretation of data, have drafted the work and substantively revised it and have approved the submitted version.

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