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ABOUT COVER

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REVIEW

Post-COVID-19 persistent olfactory, gustatory, and trigeminal chemosensory disorders: Definitions, mechanisms, and potential treatments

Sherifa Ahmed Hamed

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Abstract

The nose and the oral cavities are the main sites for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into the body. Smell and taste deficits are the most common acute viral manifestations. Persistent smell disorders are the most common and bothersome complications after SARS-CoV-2 infection, lasting for months to years. The mechanisms and treatment of persistent post-coronavirus disease 2019 (COVID-19) smell and taste disorders are still challenges. Information sources for the review are PubMed, Centers for Disease Control and Prevention, Ovid Medline, Embase, Scopus, Web of Science, International Prospective Register of Systematic Reviews, Cumulative Index to Nursing and Allied Health Literature, Elton Bryson Stephens Company, Cochrane Effective Practice and Organization of Care, Cooperation in Science and Technology, International Clinical Trials Registry Platform, World Health Organization, Randomized Controlled Trial Number Registry, and MediFind. This review summarizes the up-to-date information about the prevalence, patterns at onset, and prognoses of post-COVID-19 smell and taste disorders, evidence for the neurotropism of SARS-CoV-2 and the overlap between SARS-CoV-1, Middle East respiratory syndrome coronavirus, and SARS-CoV-2 in structure, molecular biology, mode of replication, and host pathogenicity, the suggested cellular and molecular mechanisms for these post-COVID19 chemosensory disorders, and the applied pharmacotherapies and interventions as trials to treat these disorders, and the recommendations for future research to improve understanding of predictors and mechanisms of these disorders. These are crucial for hopeful proper treatment strategies.

Key Words: COVID-19; SARS-CoV-2; Coronaviruses; Olfactory and gustatory chemosensory disorders; Anosmia; Ageusia; Parosmia; Neuronal degeneration; Neurogenesis

Core Tip: Smell loss is the most frequent acute manifestation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Persistent smell disorders (deficits and distortions) are the most frequent viral complications. Taste and flavor disorders are also complications of SARS-CoV-2 infection but at lower frequencies compared to smell disorders. It has been found that SARS-CoV-2 has a 4 times more affinity to infect the olfactory epithelium compared to other human coronaviruses. The mechanisms of these disorders have been explored mainly based on animal models of anosmia due to SARS-CoV-2 infection. It has been suggested that the post-coronavirus disease 2019 transient smell loss might be due to viral infection to the olfactory non-neuronal epithelial cells (particularly the susentacular cells) which are important for the health of olfactory sensory neurons (OSNs). These cells rapidly regenerate after injury, within 1-3 wk, and restore smell function. Persistent smell disorders have been suggested to be due to injury of OSNs, disorganization of the olfactory epithelium, altered expression of olfactory receptors, and impaired olfactory neurogenesis. These cells require ≥ 3 mo to regenerate and restore function depending on the severity and type of injury. Taste disorders have been suggested to be due to viral infection of taste buds, disruption of the activity of the salivary glands, inflammation of the gustatory epithelium, and injury to the taste sensory cells. Treatment of these disorders is a medical challenge, and none of the available pharmacotherapies or interventions which are used to treat similar disorders due to other causes, showed curative effect.

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INTRODUCTION

Increasing data and meta-analyses reported a high prevalence of smell loss (anosmia/hyposmia) as an acute manifestation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (40%-86%)[1]. It has been reported that smell loss (anosmia/hyposmia) could be the hallmark or an isolated symptom of SARS-CoV-2 infection without other viral manifestations in 25%-44% of patients[1,2]. True taste loss (ageusia/hypogeusia) has been estimated to occur in 10.2%-42% of patients due to SARS-CoV-2 infection[1-3]. True nasal trigeminal chemosensory loss has been estimated to occur in 20%-33% of patients due to SARS-CoV-2 infection[4].

Long-lasting or persistent smell disorders (deficits and distortion), lasting for ≥ 6 mo, are the most common complications of SARS-CoV-2 infection with an estimated prevalence of ~20%-40%[1,5,6]. Parosmia is the most frequent type of smell distortions, occurring in 65% of patients after an interval of a month or more from the onset of smell loss or resolution of other acute viral manifestations. A few studies reported phantosmia in 20% of patients[7]. Distortions of taste (dysgeusia) or flavor (aroma) perception have been reported in ~12%[3].

There have been no systematic studies which determined the course of smell and taste disorders after SARS-CoV-2 variants. Hintschich *et al*[8] reported that the wild type SARS-CoV-2 was associated with a higher prevalence of hyposmia (73%) according to patients' self-reports and psychophysical testing compared to the alpha (41%) or delta (48%) variants. Boscolo-Rizzo *et al*[9] observed that 30% of patients infected with the omicron variant had olfactory dysfunction. Vihta *et al*[10] reported smell loss in 13%-16% of patients during the dominant period of omicron variant infection compared to 44% when the delta variant pandemic was dominant. The authors suggested that the difference in the omicron spike protein might result in less effective cell membrane fusion and host olfactory cell entry. However, the increase in the prevalence of chemosensory disorders after omicron infection has been suggested to be due to the fact that the transmission of omicron variant is 4-fold higher compared to the delta variant [11].

Information sources for the review are PubMed (https://www.ncbi.nlm.nih.gov/research/coronavirus/), the Centers for Disease Control and Prevention, Ovid Medline, Embase, Scopus, Web of Science, International Prospective Register of Systematic Reviews, Cumulative Index to Nursing and Allied Health Literature, Elton Bryson Stephens Company, Cochrane Effective Practice and Organization of Care, Cooperation in Science and Technology, International Clinical Trials Registry Platform, World Health Organization, United States National library of Medicine, Cochrane ENT Trials Register, Randomized Controlled Trial Number Registry, and MediFind. A manual search was also done for additional information. Search words were SARS-CoV-2, coronavirus disease 2019 (COVID-19), coronaviruses (CoVs), β-CoVs, neurotropism, smell, taste, flavor, trigeminal chemosensation,

olfactory sensation, gustatory sensation, olfactory neuronal regeneration, post-COVID-19 syndrome, anosmia, ageusia, parosmia, dysgeusia, and long-lasting or persistent post-COVID-19 chemosensory disorders. In this review, we discuss the prevalence of post-COVID-19 chemosensory disorders, their patterns and prognoses, the cellular and molecular mechanisms underlying these disorders, and the potential pharmacotherapies and interventions for their correction. A brief background about the olfactory and gustatory pathways, perceptual processes, and neuronal degeneration/regeneration is provided to facilitate readers to understand the pathophysiology underlying these disorders secondary to viral infection.

BACKGROUND

Nasal chemosensation

Smell sensation is carried out by three chemosensory systems[12]: (1) The main olfactory system which carries out perception of volatile odorants; (2) the accessory olfactory system which carries out perception of non-volatile substances. These substances are not consciously perceived as odors. They include pheromones or hormone metabolites as sweat, urine, seminal fluid, and vaginal secretion; and (3) the trigeminal olfactory system that carries out perception of pungent sensations (*i.e.,* with irritant components).

There are two routes for volatile odor perception: The orthonasal and retronasal routes. In orthonasal perception, the odor molecules (also known as scents) enter the nasal cavity through the nostrils after sniffing and then to the olfactory sensory epithelium. In retronasal perception, the odor molecules of foods and drinks are transported back to the nasopharynx after swallowing or during respiratory exhalation and then to the olfactory sensory epithelium (Figure 1). Retronasal olfaction contributes to the flavor of foods or drinks (the aroma perception). It is associated with taste sensation[13].

The olfactory information is carried out from the olfactory neuroepithelium, nerves, bulb, and brain. The olfactory mucosa is composed of the olfactory epithelium and the underlying lamina propria. The olfactory epithelium has olfactory sensory neurons (OSNs) and non-neuronal cells. OSNs are bipolar cells. The bipolar cell has dendrites at one end with hair-like cilia extending to the mucus lining the nasal cavity and the other end has a single apical axon which projects directly to a glomerulus in the olfactory bulb. The olfactory receptors are odor binding G protein-coupled that are expressed in the membranes of the bipolar cell dendrites[14] (Figure 2A). The axons of the bipolar cells are the olfactory nerve fibers[15]. It has been observed that a single odorant molecule has specific chemical properties to either bind to a selective receptor or a number of receptors[14]. The olfactory epithelium is spatially organized into non-overlapping zones in which each is dominated by a certain set of odor receptors, meaning that a specific odor molecule activates a specific zone within the epithelium but not others. The normal olfactory function requires highly regulated projections from sensory neurons and regrowth of nascent axons *en masse* onto the olfactory bulb for proper integration of olfactory signals in the olfactory cortex[16]. Therefore, the same topographical mapping is maintained in the glomeruli and bulb since formed during development and throughout life (Figure 2A and B). The glomerular map is important as the glomeruli act as organizers for the odorant signals before sending them to the brain for odor detection, recognition, and discrimination[17]. Within the glomerulus, the axon of the bipolar neuron synapses with the mitral and tufted cells along with periglomerular cells (Figure 2A).

The olfactory non-neuronal cells include the sustentacular (also known as supporting cells), microvillar, Bowman's gland, and horizontal basal (stem) cells (Figure 2A). These cells, the nasal respiratory epithelial cells, and the vascular pericytes are important for the health of OSNs. Sustentacular cells surround and support OSNs, detoxify harmful molecules, and maintain epithelial salt and water balance[18]. The Bowman's glands secrete mucous[18]. The mucus contains large concentrations of small soluble proteins which keep odorant molecules dissolved in the mucus. The odorant-protein complexes bind to the receptors[15]. The microvillar cells (also known as brush cells) help in protection of OSNs by stimulating the sustentacular cells to metabolize and detoxify harmful molecules [19], and have a role in adjustment of ion gradients which is important for maintenance of the function of OSNs, and their basal surfaces are in contact with afferent nerve endings of the trigeminal nerve for transduction of nasal general sensation[18]. Basal cells are multipotent stem cells that undergo continuous division during life to produce new OSNs and non-neuronal epithelial cells, *i.e.,* endogenous regeneration process[18,20].

In the process of olfaction, the chemical information of the odorants converts into electrical information. The odorant molecules trigger a signaling cascade which includes activation of the cyclic nucleotide-gated ion channels followed by activation of adenylyl cyclase type 3 (ADCY3). ADCY3 is localized into the cilia of OSNs. ADCY3 activation is an essential component to convert adenine triphosphate to cyclic adenine monophosphate (cAMP) (*i.e.,* the olfactory cAMP signaling pathway) [21]. cAMP unfolds ion channels resulting in influx of calcium (Ca^{++}) and sodium (Na^{+}) inside the cell. This opens Ca^{++}-activated chloride (Cl^{-}) channels leading to outflow of Cl^{-}, resulting in neuronal membrane depolarization and propagation of action potential from the olfactory epithelium to the bulb and then the brain[22] (Figure 3). The primary olfactory cortical areas include the uncus, anterior

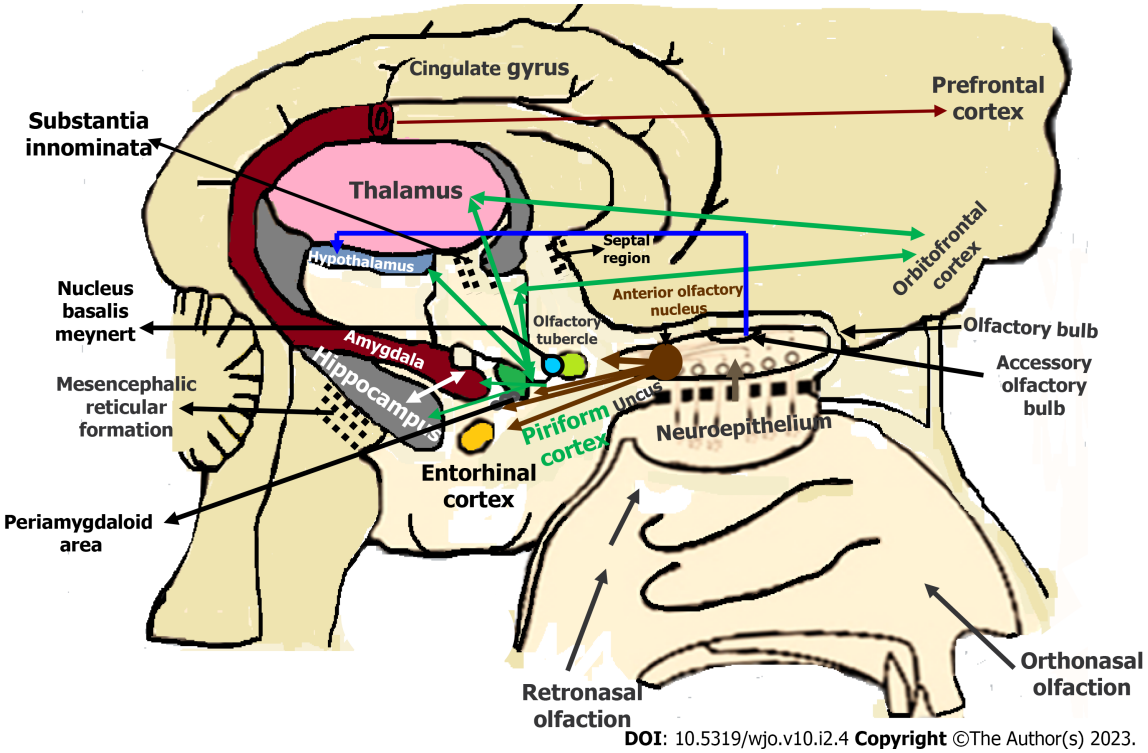

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Figure 1 Olfactory perception and its pathways. There are two routes for odor perception: The orthonasal and retronasal routes. The process of olfaction converts chemical information from odorants into electrical potentials extending from the olfactory epithelium to the bulb and then the brain. Brain areas for perception of olfaction sensation are divided into the primary and the secondary cortical olfactory areas. The primary areas include the uncus, anterior olfactory nucleus, olfactory tubercle, piriform cortex, lateral entorhinal cortex, and the cortical nucleus of the amygdala. The secondary areas include the hypothalamus, mediodorsal thalamic nucleus, nucleus basalis Meynert, hippocampus, the septal region, substantia innominata, mesencephalic reticular formation, and the orbitofrontal cortex.

olfactory nucleus, piriform cortex, lateral entorhinal cortex, olfactory tubercle, and cortical nucleus of the amygdala[23]. The primary olfactory cortex projects to the secondary olfactory cortical areas for further processing of olfactory impulses as odor perception, discrimination, attention, memory, and motivational and emotional aspects of smell. These areas are the hypothalamus, mediodorsal thalamic nucleus, nucleus basalis Meynert, hippocampus, septal region, substantia innominata, mesencephalic reticular system, and orbitofrontal cortex[24] (Figure 1).

The trigeminal chemosensation allows the perception of pungent, irritant, burning, stinging, tickling, and noxious chemicals odorants even in the absence of olfactory sensation[25] and triggers the protective respiratory reflexes (as sneezing and coughing). This system relies on free nerve endings and on the trigeminal-innervated solitary chemosensory cells (SCCs) in the nasal epithelium. The free nerve endings recognize the lipophilic irritant odors (as mints and ammonia) while the SCCs enhance the chemosensory capabilities of the trigeminal irritant-detection system through expression of certain receptors for detection of noxious chemicals[26].

It has been reported that the olfactory and trigeminal systems are intimately connected at peripheral (*i.e.*, nasal mucosa) and central (the piriform cortex, the ventral insula, and the frontal cortex) levels[27, 28].

Oral chemosensation

Till now, the five known chemical structures that taste sensing cells can detect are sweet (sugar), salty (salt), sour (lemon juice), bitter (unsweetened decaffeinated coffee), and umami or savory (proteins as meet and aged cheese). Everything else is known as flavor which is the function of retronasal olfaction [29,30]. All regions of the tongue that detect taste respond to all the five taste qualities; however, it has been observed that the sensations of sweet and salt are best detected in the tip of the tongue. The highest concentrations of bitter receptors are in the posterior tongue[31] (Figure 4A). Tastants are detected by specialized receptor cells within the taste buds of the tongue, soft palate, and epiglottis. In the tongue, taste buds are located within the tongue papillae[29]. Most papillae have 3-5 taste buds, but some types of papillae have thousands of taste buds. The taste bud has taste sensing cells and non-neuronal cells. The taste sensing cells express specific receptors[32]. The taste receptor cells are arranged within the bulb in a manner that their tips form a small pore in which the microvilli or hair-like projections extend to the saliva layer within the oral cavity. The saliva interacts with and protects the taste receptors in the mouth. For the transduction of taste stimuli, the molecules of food or drink must be dissolved in the saliva[30] (Figure 4B). A single taste bud has 50 to 100 taste cells, among which there are 10 and 50 taste

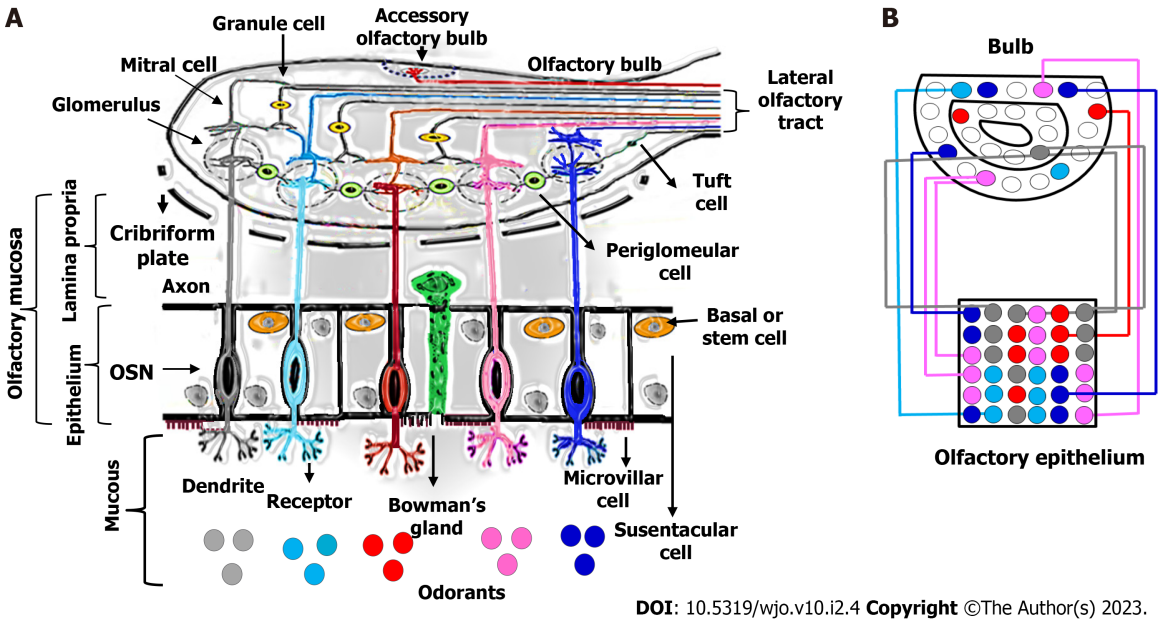

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Figure 2 Structure of the olfactory mucosa and topographical mapping of the olfactory sensory neurons and their connections. A: The olfactory mucosa is composed of the olfactory epithelium and the lamina propria. The epithelium is composed of olfactory sensory neurons and non-neuronal cells (the susentacular, microvillar, and Bowman's gland and basal cells). A bipolar cell has dendrites at one end extending to the mucus and a single axon which projects to the glomerulus. Within a glomerulus, the axon of the bipolar neuron synapses with the mitral and tufted cells along with periglomerular cells; B: The olfactory neurons which express the same type of receptors converge onto the same glomerulus maintaining a topographical mapping of odorant receptors where they synapse with sensory neurons of the olfactory tract. The same topographical mapping is maintained in the glomeruli and bulb.

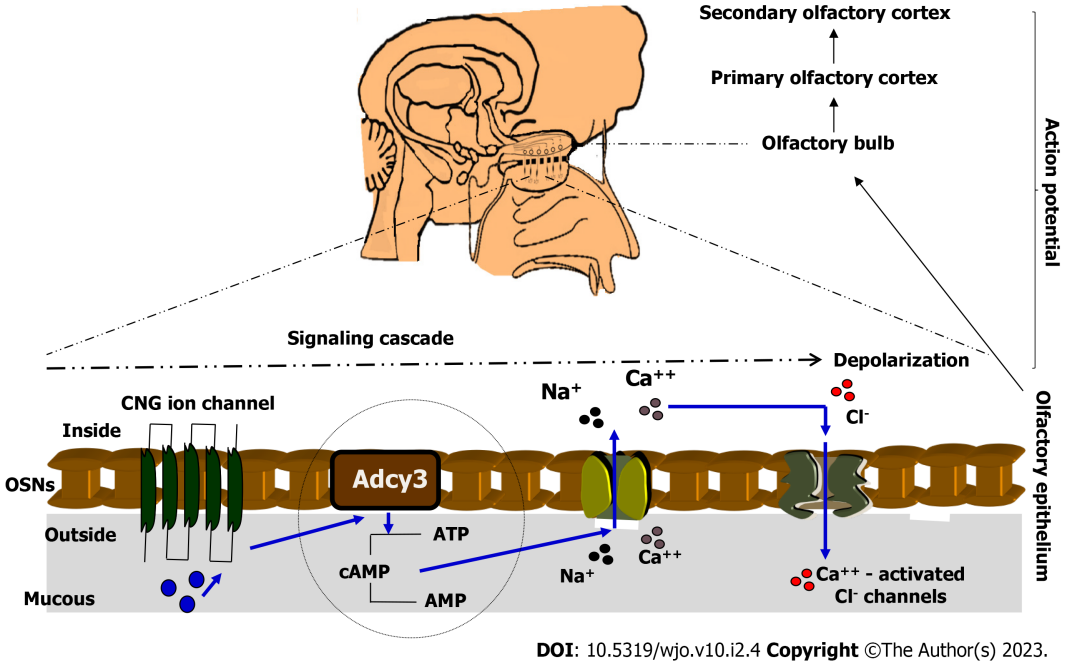

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Figure 3 The process of olfaction. The signaling cascade which converts chemical information of the odorant into electrical information includes activation of cyclic nucleotide-gated ion channel followed by activated ADCY3 to convert ATP to cyclic adenine monophosphate (cAMP). cAMP unfolds Ca^{++} activated Cl^- channels, causing influx of Na^+ and Ca^{++} from outside to inside the olfactory sensory neurons, and this activates the Cl^- channels, causing outflow of Cl^-, neuronal membrane depolarization, and the action potential. The latter extends from the epithelium to the bulb and then to the olfactory cortex.

sensory cells. The non-neuronal cells include the supporting cells and the basal cells. The basal cells are stem cells which actively divide throughout life into taste sensory cells and accessory gustatory epithelial cells (Figure 4A and B).

In the process of gustation, the tastant molecules are connected to their specialized receptors and upon doing so, activation of nerve impulses occurs and the receptors release neurotransmitters which activate sensory neurons in the facial, glossopharyngeal, and vagus cranial nerves. The taste information

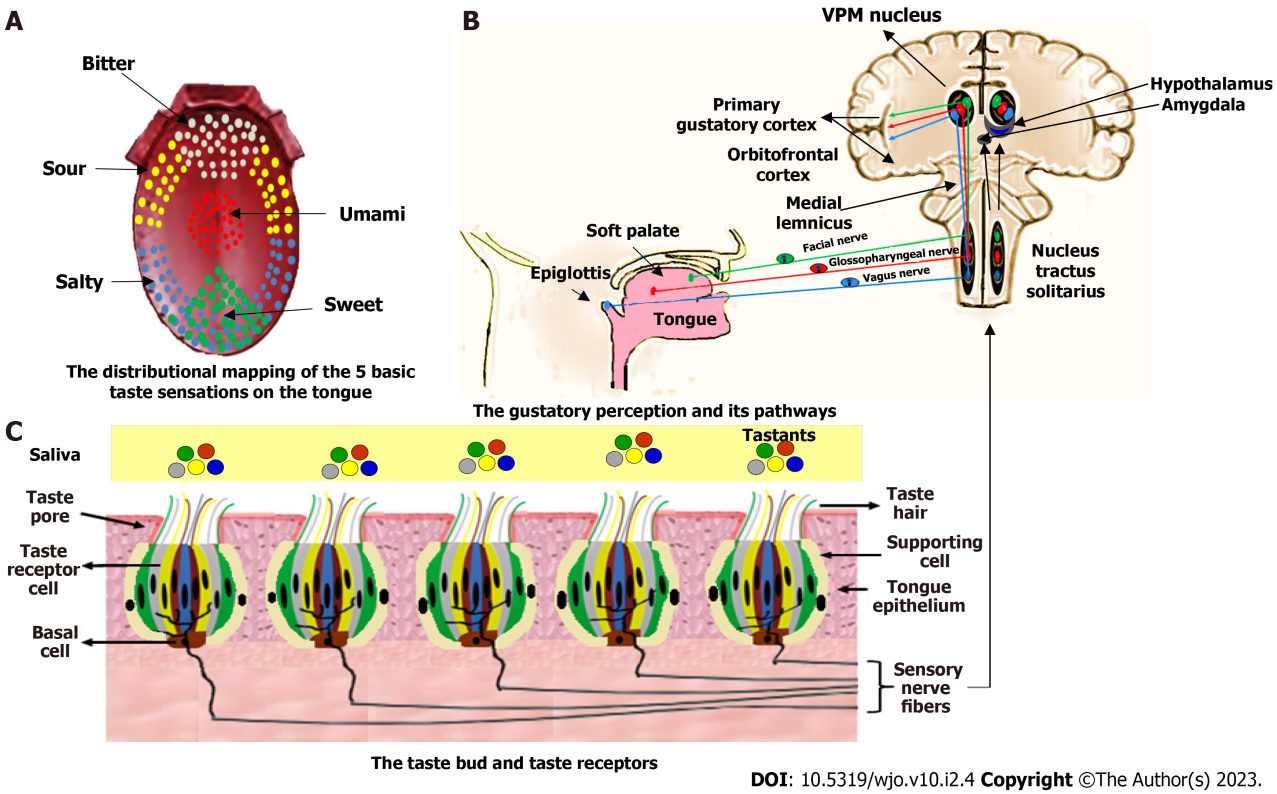

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Figure 4 Distributional mapping of the five basic taste sensations on the tongue, the gustatory pathways, and the taste bud and receptors. A: The five basic taste qualities are sweet, salty, sour, bitter, and umami; B: Tastants are detected by the taste buds on the tongue, soft palate, and epiglottis. Activation of taste receptors is transmitted to the sensory neurons in the facial, glossopharyngeal, and vagus cranial nerves from which their axons carry information to the nucleus solitaries in the medulla oblongata, to the ipsilateral ventral posteromedial nucleus of the thalamus, and then to the primary gustatory cortex. The nuclei in the medulla also send projections to the hypothalamus and amygdalae to activate brainstem reflexes. Secondary fibers project from the insula to the posterolateral portion of the orbitofrontal cortex; C: The taste bud has taste sensory and supporting cells. The taste receptors have long microvilli or hairs which project through the taste pore to connect with substances in the food or drink dissolved into the saliva. VPM: Ventral posteromedial.

is carried out to the nucleus solitarius in the medulla oblongata, the ipsilateral ventral posteromedial nucleus of the thalamus, and then the primary gustatory cortex which includes the frontal operculum or anterior insular cortex located near the inferior margin of the post-central gyrus. The nuclei in the medulla also send projections to the hypothalamus and amygdalae, which are involved in autonomic reflexes such as gagging and salivation[32]. The primary gustatory cortex is important for discrimination of taste sensations. It also receives information about the smell and texture of food. The secondary fibers travel from the primary gustatory cortex to the posterolateral portion of the orbitofrontal cortex for integration of taste and smell sensations (Figure 4).

Studies found that the orally sourced odors share processing circuitry with taste and internal odors to produce flavor preferences. They found that inactivation of the insular gustatory cortex impaired selectively the expression of retronasal preferences[13]. Trigeminal chemosensation is also considered a part of flavor perception[32].

Endogenous neurogenesis processes of olfactory and gustatory cells

The olfactory and gustatory neurons in the human body are the only types of neurons that are regularly replaced within the nasal and oral epithelia throughout life by newly generated neurons as a part of the turnover process (*i.e.*, life-long olfactory and gustatory sensory neurogenesis)[33]. Replacement of olfactory neurons occurs at 4-12 wk intervals[16,33]. The gustatory receptor cells are short-lived and replaced every 10 d[34]. This process has been understood to happen because the olfactory mucosa can be easily harmed by airborne and toxic chemicals and viruses, and the gustatory mucosa can be easily damaged by the activities that occur in the mouth. A reconstitution of the sensory epithelium occurs from the stem cells with a subsequent restoration of olfactory function. This process requires a complex signaling system, neurotropic factors, neurotransmitters, *etc.* After injury, the regeneration and restoration of olfactory receptors and their connections depend on the degree and type of injury. In many circumstances, the olfactory system overcomes many obstacles encountered when rewiring the olfactory bulb after olfactory neuroepithelial injury, and can be able to maintain its capacity to regenerate new axon processes and reestablish functional connections within the olfactory bulb[16].

Investigators observed that when injury was limited to the olfactory neuroepithelium sparing the olfactory nerves, the regenerating new axons grew along the axons that were already in place, and the newly rewired connections converged onto the glomeruli in specific areas maintaining the glomerular topographical mapping of odorant receptors and re-established the functional connections with the olfactory bulb[35]. It has been discovered that stabilization of olfactory receptor expression and guidance and stabilization of the axonal growth of OSNs require ADCY3[36-38]. However, if injury involved the olfactory neuroepithelium and nerves, there was a competition among the regenerating axons to occupy synaptic sites within a glomerulus, with inability of the glomerulus to be dominated by a single odorant, resulting in impaired odor discrimination and anosmia and dysosmia[39-41] (Figure 5A and B). Those authors also observed that long-lasting anosmia can alter the integrity of the mitral and tufted cell dendrites. Murai *et al*[42] observed reduced connectivity of mitral/tufted cell dendrites and attenuated odor responses in these cells after olfactory neuronal injury.

PATTERNS AND PROGNOSES OF SMELL AND TASTE DISORDERS WITH SARS-CoV-2 INFECTION

Studies reported two main patterns for smell loss (with or without taste or flavor loss) as an acute manifestation of SARS-CoV-2 infection: (1) Sudden smell loss (anosmia/hyposmia) in association with general, systemic, or other ear, nose, and throat manifestations. Anosmia is the term used to define the absence or loss of the sense of smell. Hyposmia is the decreased sense of smell. This is the most frequent pattern. It has been reported that smell loss occurs either at the same time with other viral manifestations (22.8%-88.0%)[1,2], after the recovery of other viral manifestations (26.6%-65.4%)[1,2], or before the onset of other manifestations (11.8%)[2]; and (2) Isolated smell loss without any other viral manifestations (~16%-19.4%)[43].

Clinical studies reported that the most frequent other acute nasal symptoms of SARS-CoV-2 infection are dryness, itching, nasal burning, and sneezing, occurring in 75%-87% of patients, while nasal congestion and blockage and anterior nasal discharge (rhinorrhea), which are the main symptoms due to other viral infections of the upper respiratory tract (*e.g.*, influenza), are rare with SARS-CoV-2 infection, occurring in only 12.9%-25%[2,44,45].

Some authors observed a mismatch between subjective and objective smell and taste manifestations at onset. The high frequency of subjective anosmia and ageusia compared to the low frequency of true ageusia detected by objective evaluation (40%-86% *vs* 10.2%-42%), is not surprising. The belief that taste will be lost with smell loss is based on the fact that the ability to perceive flavors is adversely affected by the concomitant presence of smell loss[46].

The majority of studies reported the presence of true ageusia exclusively in patients with anosmia, while ageusia without anosmia was rarely reported[3,47]. Loss of flavor of food and drinks (aroma perception) is also an infrequent manifestation of SARS-CoV-2 infection but has been found to be always dependent on the presence of ageusia but not anosmia[3]. Subjective sudden loss to pungent or irritant odors and tastants (*e.g.*, mint gum, black pepper, ginger, and spice) has been frequently reported with severe smell loss after SARS-CoV-2 infection[4,48]. However, true nasal trigeminal chemosensory loss due to SARS-CoV-2 infection, as detected by objective evaluation, has been reported in only 18%-20% and exclusively reported in association with anosmia[4]. True oral trigeminal chemosensory loss has been reported in 20%-33% and exclusively reported in association with ageusia[4].

Studies also reported two prognoses for these disorders. They are: (1) Transient deficits which resolve within days to weeks after onset (mean: ~20 d). This is the most frequent prognosis occurring in 60%-80% of patients[49,50]; and (2) Long-lasting/persistent disorders (deficits and distortions) lasting for months to years, occurring in 20%-40%[49]. Many studies reported that the diagnosis of mild COVID-19 at onset would predict the prognosis of persistent smell disorders. Lechien *et al*[2] reported that the persistent smell disorders were prevalent in patients with isolated conditions or if associated with mild COVID-19 manifestations (86%-95% *vs* 4.5%-10% with moderate/severe manifestations). However, the increasing number of published studies has shown that none of the demographics, acute manifestations, and severity at onset were predictors of the development of persistent disorders[1,5].

Dysosmia is a frequent manifestation (~75%-80%) in patients with persistent post- COVID smell loss. Dysosmia is a qualitative or distortion of perception of an odor. It is another smell or a strange sensation (pleasant or unpleasant) of inhaled odorants. Dysosmia often develops after a month or more from the onset of acute manifestations or smell loss[2,44]. Parosmia is the frequently encountered type of smell distortion after SARS-CoV-2 infection, occurring in 65% of patients. Parosmia is defined as perception of an odor in the presence of odorous source[7]. Some patients would develop an excessively unpleasant repulsive, unbearable, disgusting, or intolerable odor (cacosmia). A few studies reported the occurrence of phantosmia in patients with persistent post-COVID-19 anosmia (20%). Phantosmia is defined as distortion of smell perception in which there is a perception of an odor in the absence of odorous source [7]. Dysgeusia or distortion of taste and distortion of aroma[3] were only reported in patients with persistent post-COVID taste loss (~12%-20%). Common descriptions for parosmia or dysguesia or distortion of flavor included burnt (like burnt hair or burnt leather), rotten (as spoiled or fermented

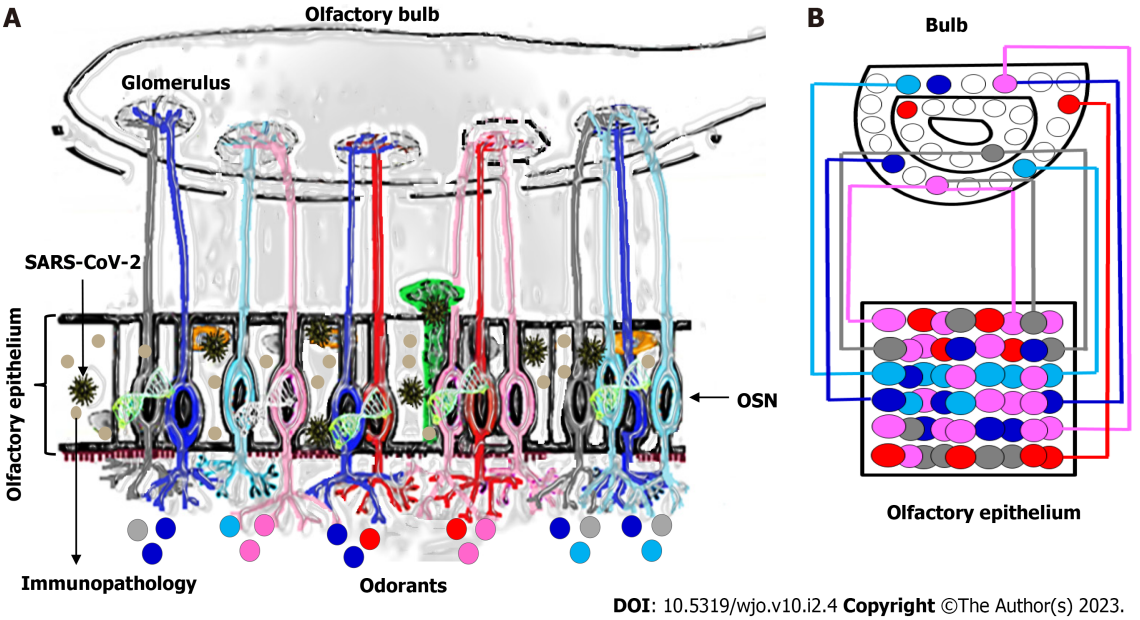

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Figure 5 Mechanism of dysosmia after severe acute respiratory syndrome coronavirus 2 infection. A: The disorganized olfactory neuroepithelium after severe acute respiratory syndrome coronavirus 2 infection and its associated immunological response would result in a disturbance of rewiring of the glomeruli; B: A glomerulus is no longer dominated by a single type of odor and the newly growing axon after injury would go to a different brain spot other than the one before injury, resulting in a distorted sense of smell.

food), gasoline, fecal, smoke or metallic (like copper), chemical (like sulphur), *etc*. However, many described the unpleasant unknown odor which was difficult to describe (*i.e.*, new)[7].

Magnetic resonance imaging (MRI) had been used for evaluation of olfactory structures and connections after SARS-CoV-2 infection in patients with anosmia. However, findings were limited and conflicting. Some found olfactory bulb edema and/or olfactory cleft edema in patients with anosmia, suggesting local inflammation and a greater local immune response[51-56]. Some authors reported microbleeding or a break in the blood-brain barrier (BBB) of the olfactory bulbs and tracts[57,58]. Kandemirli *et al*[59] reported a high percentage of abnormal olfactory bulb signal intensity and contour changes in cases with persistent COVID-19 anosmia (n = 23). Yildirim *et al*[60] used MRI, digital tensor imaging, and olfactory functional MRI for evaluation of patients. They found decreased olfactory bulb volume, indicating bulb damage and decreased white matter tract integrity of the olfactory regions. The authors evaluated the olfactory bulb in patients with persistent post-COVID-19 olfactory disorders (n = 31, 100% were anosmic and had a mean interval of 1.5 mo between onset of olfactory disorder and imaging) and patients with other post-infectious olfactory disorders (n = 97, among which 18.6% were hyposmic and 81.4% were anosmic and had a mean interval of 6 mo between onset of olfactory disorder and imaging). Compared to patients with post-infectious olfactory disorders, the authors found significantly higher volumes of olfactory bulbs in patients with persistent post-COVID-19 olfactory disorders, deformed bulb morphology in 58.1% (*vs* 63.9%, with no significant difference), increased olfactory bulb signal intensity in 51.6% (*vs* 46.4%, with no significant difference), and a significantly higher rate of olfactory nerve clumping and anisotropy values at orbitofrontal and entorhinal regions but no significant difference had been identified between the two groups in the orbitofrontal and entorhinal activity apart of the robust trigemino-sensory activity in patients with persistent post-COVID-19 olfactory disorders but not in those with other post-infectious olfactory disorders.

NEUROTROPISM POTENTIALS OF COVS AND ROUTES FOR VIRAL SPREAD TO NERVOUS TISSUE WITH SPECIAL EMPHASIS ON SARS-COV-1, MIDDLE EAST RESPIRATORY SYNDROME-COV, AND SARS-COV-2

There are two known groups of human CoVs (HCoVs): (1) α-CoVs which include HCoV-229E (named after a student specimen coded 229E) and HCoV-NetherLand 63 (NL63)[61]; and (2) β-CoVs which include HCoV-Hong Kong University 1 (HKU1), HCoV-Organ Culture 43 (OC43), SARS-CoV-1, Middle East respiratory syndrome (MERS)-CoV, and SARS-CoV-2[61]. HCoV-229E, HCoV-NL63, HCoV-HKU1, and HCoV-OC43 induce mild and spontaneously resolved (*i.e.*, transient) respiratory symptoms such as rhinitis, sore throat, and dry cough similar to common cold or enteric and systemic manifestations[62]. SARS-CoV-1[63], MERS-CoV[64], and SARS-CoV-2[65] are dangerous CoVs. SARS-CoV-1 was firstly

identified in China in 2002-2003. MERS-CoV was firstly identified in Saudi Arabia in 2012. SARS-CoV-2 was firstly identified in Wuhan, China in December 2019[65]. They are the causes of severe and potentially fatal respiratory tract infections and the known three worldwide pandemics[61,66]. Human neurotropic CoVs are CoV-229E, CoV-OC43, SARS-CoV-1, MERS-CoV, and SARS-CoV-2[63,64].

In general, CoVs are frequently recognized as respiratory pathogens[67]; however, some have neuroinvasive and neurotropic properties[61]. In animal models, some authors detected that some CoVs spread to the brain using the neuronal pathway (*i.e.*, peripheral trigeminal or olfactory systems) or through disruption of the BBB. In the mouse model, Perlman *et al*[68] found that ablation of the olfactory pathway did not allow the neural spread of CoVs. Hara *et al*[69] found that the viral particles of hemagglutinating encephalomyelitis virus, a member of β-CoVs, bud into the endoplasmic reticulum-Golgi cells and form virion vesicles into Golgi cells, followed by secretion into the surroundings and infection of adjacent nerve cells[70]. Koyuncu *et al*[71] reported nasal mucociliary transport and disruption of the ciliary nasal epithelium with HCoV-229E[72]. Mori *et al*[40] found entry of CoVs to the central nervous system through the olfactory tract in earlier stages of viral infection. Dubé *et al*[73] detected HCoV-OC43 in the piriformis cortex, brainstem, and spinal cord by the fourth day after nasal viral inoculation and indicated that HCoV-OC43 can propagate from neuron to neuron through axonal transportation. Netland *et al*[74] detected SARSCoV1 in mice expressing human angiotensin-converting enzyme 2 (ACE2) in the olfactory bulb after 60 h of nasal viral inoculation. They also found the virus after four days of inoculation in the pyriform cortex, ventral pallidum, and lateral preoptic regions in the basal ganglia and dorsal nucleus of Rafe in the midbrain. However, the authors did not look for a potential infection of the olfactory mucosa for being the route of SARS-CoV-1 to the brain, *i.e.*, where these neurons project. Li *et al*[75] found MERS-CoV in the brain of mice expressing human CD26/dipeptidyl peptidase 4, particularly the thalamus and brainstem after nasal viral inoculation. Bryche *et al*[76] observed damage and desquamation of the olfactory sensory epithelium and loss of cilia in golden Syrian hamsters as early as 2 d after nasal inoculation of SARS-CoV-2. The authors observed infection of a large proportion of sustentacular cells but not OSNs or bulbs. Yinda *et al*[77] found SARS-CoV-2 in K18-hACE2 mice in the olfactory bulb and the connected brain areas after nasal viral inoculation. Those authors also found that the taste receptors of the gustatory sensory epithelium were targets for SARS-CoV-2 to enter and infect the body[78]. Hematogenous spread of the viruses to the brain has been found in influenza and other coronaviruses[71]. In a mouse model, Bleau *et al*[79] found that hepatitis coronavirus had the ability to cross the BBB and infect the brain. Some authors suggested that the observed brain hemorrhage or microbleeding in some patients after SARS-CoV-2 infection could be attributed to disruption and increase in the permeability of the BBB caused by the virus[80].

In autopsies of infected individuals, studies reported the presence of CoVs particles in neuronal and glial cells and brain endothelial capillary pericytes. Ding *et al*[81] found SARS-CoV-1 particles in the cerebral hemispheres. Steardo *et al*[82] detected SARS-CoV-2 antigens in the nucleus solitarius and the nucleus ambiguous in the brainstem. Coolen *et al*[83] detected SARS-CoV-2 particles in only the olfactory bulbs in early postmortem study of infected patients with anosmia. Solomon *et al*[84] used immunohistochemistry, electron microscopy, and real-time reverse transcription polymerase chain reaction (RT-PCR) in their investigations. The authors found SARS-CoV-2 particles in the olfactory epithelium and bulb. Lee *et al*[85] used high-field MRI to examine brain tissue of dead patients. The authors found microvascular damage consistent with endothelial activation and widespread vascular injury due to viral spread to the brain.

It has been found that SARS-CoV-1, MERS-CoV, and SARS-CoV-2 have close relation to each other and to animal neurotropic CoVs in structure, molecular biology, mode of replication, and host pathogenicity[86]. SARS-CoV-1 (26 kb), MERS-CoV (32 kb), and SARS-CoV-2 (30 kb) have the largest genome among RNA viruses[66]. SARS-CoV-2 has 79.5% identical RNA sequence to SARS-CoV-1 and 96% identical RNA sequence to bat CoV[62,65,66]. SARS-CoV-2 has a similar 3D structure and homology of the trimeric S proteins and their receptor biding domains as SARS-CoV-1[87]. SARS-CoV-1 [63,88,89], MERS-CoV[64], and SARS-CoV-2[76,87,90,91] enter the body and infect similar specific olfactory sensory, nasal respiratory, and tongue epithelial cells. However, apart from olfactory and gustatory chemosensory disorders after SARS-CoV-2 infection, several studies observed that SARS-CoV-2 infection did not directly infect the brain and did not follow the same pathway as SARS-CoV-1. They found that anosmia due to SARS-CoV-2 infection did not correlate with encephalopathies observed in some infected patients[80,92-94]. Also many studies did not detect SARS-CoV-2 RNA by RT-PCR in the cerebrospinal fluid from living patients who were infected with SARS-CoV-2 and had neuropsychiatric manifestations[94]. Investigators suggested that the non-specific acute symptoms such as disturbed consciousness, delirium, encephalopathy, lack of concentration, fatigue, headache, and generalized weakness could be attributed to the acute severe illness with respiratory and metabolic disturbances or as a non-specific cellular immune or antibody-mediated phenomenon (*i.e.*, peri- or postinfectious processes or a para-infectious cytokine storm)[94,95]. Some authors suggested that SARS-CoV-2-related encephalopathy could include interruption of the BBB and microbleeding, brain hemorrhage[80,96], or clotting abnormalities[92].

CELLULAR AND MOLECULAR MEBHANISMS OF SARS-COV-2 INDUCED SMELL AND TASTE DISORDERS

Mechanism(s) of anosmia

Evidence from most studies indicates that the nose is the main site for SARS-CoV-2 entry to the body and the site for viral shedding during the incubation period. Virus shedding is the phase in which the virus reproduces and exports a large amount of copies[93]. It has been indicated that post-COVID-19 smell loss is not solely related to nasal inflammation associated with mucosal edema, and airflow obstruction as in other upper respiratory infections[44]. Experimental studies found that SARS-CoV-2 mainly infects the olfactory non-neuronal epithelial cells (susentacular cells, microvillar, mucin secreting, and basal cells), nasal vascular pericytes, and the nasal respiratory epithelium[97]. Previous studies also reported that SARS-CoV-1 and MERS-CoV enter the body from the supporting olfactory sensory epithelial cells, the nasal respiratory epithelial cells particularly the susentacular cells, and the pericytes of the olfactory bulb[61]. These cells, particularly the susentacular cells, are overloaded by ACE2 receptors[76,90,93]. The virus infects these cells through interaction between its spike glycoprotein (S) and ACE2 protein on target cells. This interaction requires cleavage of the S protein by transmembrane serine protease 2. In a golden Syrian hamster model of SARS-CoV-2 infection, investigators found viral infection of a large amount of sustentacular cells within the first 48 h after nasal inoculation of the virus, followed by rapid and massive invasion by immune cells in the nasal mucosa. This resulted in disorganization followed by desquamation of the olfactory epithelium. The authors found the desquamated epithelium and the cilia of OSNs in the nasal cavity and a reduction of ~80% of the thickness of the olfactory epithelium. The authors did not detect the virus in OSNs or the bulb. They also observed complete absence of the virus from the nasal cavity after 7-14 d and restoration of ~50% of the olfactory epithelium[76,90]. Zhang *et al*[98] observed infection of mature and immature OSNs by the virus but to a lesser extent compared to sustentacular cells infection. Injury of the accessory epithelial cells should disturb the function of OSNs, resulting in smell deficits[99]. Injury of the sustentacular cells disturbs the support of OSNs and salt and water balance of the epithelium[99]. Injury of the Bowman's glands will disrupt nasal mucous production. The change in the mucous density and the breakdown of mucin barrier will diminish olfactory sensitivity through reduction of the number of odorant molecules that can adhere to the receptors[100], resulting in smell loss, nasal dryness[100], or distortion of smell sensation[101]. Injury to microvillar cells will disturb epithelial ion gradients[18] and impair transduction of nasal sensation[19]. It has been suggested that injury of supporting cells by the viral infection could explain the occurrence of transient anosmia at onset of viral infection in the majority of patients [47]; because these cells rapidly regenerate within 1-3 wk after degeneration[33]. This is also compatible with the observed rapid restoration, within 14 d, of ≥ 50% of the injured olfactory epithelium in hamsters infected with SARS-CoV-2[76,90].

However, long-lasting post-COVID-19 anosmia and dysosmia are due to injury of OSNs (receptors), because these cells require at least 3 mo to regenerate after injury[16]. OSNs do not express ACE2 receptors. Therefore, it is plausible to suggest that long-lasting/persistent post-COVID-19 anosmia and dysosmia could be due to severe damage and disorganization of the olfactory epithelium by viral infection and its associated immunopathology which could also include the stem cells, resulting in delay or even lack of restoration of the lost epithelial cells and reconstitution of the injured epithelium[16].

Some aspects of the molecular mechanisms of SARS-CoV-2 infection to the olfactory system have been explored in experimental models and supported the notion that injury/dysfunction of OSNs is the cause of smell disorders. Thakur *et al*[102] used the UV-neutralized serum from hamsters infected with SARS-CoV-2 to investigate the molecular mechanisms of SARS-CoV-2 induced olfactory injury and dysfunction. They found rapid changes in the nuclear architecture of OSNs. Zazhytska *et al*[91] investigated the hamster's olfactory epithelia infected with SARS-CoV-2. The authors found: (1) Widespread, severe, and persistent down-regulation of olfactory receptor genes and ADCY3, and other signaling genes for odor perception; (2) A delay in the transcription of OSNs compared to susentacular cells; (3) The disruption and down-regulation of olfactory receptors' layers occurred before the down-regulation of *LHX2* and *EBF* genes, suggesting that disruption of the olfactory receptor genome architecture may be the earliest insult in dysfunction of OSNs and SARS-CoV-2 induced anosmia. LHX2 and EBF are the transcription factors which regulate the olfactory receptor choice; and (4) The persistence of down-regulation of LHX2 and EBF even after the restoration of olfactory receptors. Investigators observed overlap in the molecular changes in the OSNs caused by different SARS-CoVs, which include: (1) Reduction in expression of genes involved in every step of odor detection including down-regulation in olfactory receptors and their signaling molecules (*e.g.*, ADCY3)[103] and reduction in olfactory receptor proteins[15]; (2) Reduction in olfactory receptor chaperones[104]; and (3) Reduction in ion channels generating odor-evoked axon potential[105].

Mechanism(s) of dysosmia

It has been suggested that the cause of dysosmia is the disorganization of the topographical mapping of the receptors or OSNs within the epithelium due to SARS-CoV-2 infection pathology (Figure 5A). Therefore, a glomerulus will not be dominated by a single type of odor and the newly growing axons

will run in different conduits and reach a different brain spot from that before injury[36-38] (Figure 5B). It has been reported that dysomia is a marker of neuronal degeneration or regeneration (*i.e.*, a step toward neuronal recovery or neuronal regeneration after degeneration) regardless of its cause (*e.g.*, after upper respiratory infections, head trauma, and nasal sinus disease)[42]. Also, it is indicated that dysosmia never exists with complete anosmia, meaning that it requires a relatively intact sensory system for its expression[106] and disappears with complete recovery of smell sensation over time or after therapy[42].

Mechanisms of ageusia

The mechanisms of post-COVID-19 true taste disorders are less understood compared to smell disorders. SARS-CoV-2 was found in the saliva of patients with viral infection[107] and viral replication has been shown to occur in human taste buds[108]. In animal models, investigators observed that SARS-CoV-2 selectively infects the tongue compared to the non-lingual epithelium. They observed that ACE2 is mainly expressed in epithelial cells outside of taste papillae which contain the taste buds[78], the human salivary gland also expresses high amounts of ACE2[109], and the tongue taste buds express sialic acid. The taste buds also express abundant amounts of Toll-like receptors (TLRs) compared to the other components of the oral cavity[110]. Sialic acid is a salivary mucin component. Mucin conveys the molecules of tastants into taste pores to prevent their premature enzymatic degradation[111]. The main function of the TLRs is to recognize the common structural components of microorganisms and activate the endogenous inflammatory immune system. Previous studies found a plethora of cytokines and chemokines in the nasal cavity and paranasal sinuses in patients with chronic rhinosinusitis and rhinitis in response against microbes[112]. Studies suggested that SARS-COV-2 potentially uses multiple entry oral receptors, which are the ACE2, sialic acid receptors, and TLRs[113]. Therefore, binding of SARS-CoV-2 to sialic acid receptors could interfere with glycoprotein mediated transport of tastants and accelerate the degradation of the gustatory particles, which contributes to loss of taste[114]. Previous studies also reported the ability of the MERS-CoV and SARS-CoV-1 to bind the sialic acid receptors on the taste buds[115]. The disruption in the activity of the salivary glands by viral infection could produce imbalance or disruption of saliva composition, impairment of salivary flow, and the continuous renewal of tongue epithelial cells, resulting in dry mouth, impairment of taste transduction, and ageusia[78,116,117]. Studies observed that SARS-CoV-2 binding with oral mucosal cells might trigger inflammation, abnormal cell turnover, and reduced taste bud sensitivity[78,118]. *In situ* models of direct binding of coronavirus spike protein with TLR1, 4, and 6 have supported the specific roles of these TLRs in CoV-2 entry and SARS-CoV-2 infection[119]. It has been suggested that inflammation could increase epithelial cell exfoliation and constitute potential sources of viral SARS-CoV-2 RNA in saliva[120,121]. Experimental studies provided evidence that inflammatory cytokines induced by viral infections could negatively affect the function of taste buds[110]. Previous findings also suggested that viral invasion to taste cells can lead to genetic material exchange between the virus and taste cell subpopulations and this could be the cause of virus-induced taste disorders[122,123].

Mechanism(s) of dysgeusia

The mechanisms of dysgeusia due to SARS-CoV-2 infection are less understood compared to parosmia. It is possible that dysgeusia could be due to the reduction of the salivary flow which normally causes continuous renewal of tongue epithelial cells[107]. We also suggest that dysgeusia could be a trial of regeneration of gustatory neuronal cells after its degeneration by viral pathology and the disorganization of taste receptors' layering within the taste buds.

Mechanism(s) of trigeminal chemosensory disorders

The trigeminal chemosensory loss after SARS-CoV-2 infection could be due to loss of smell and flavor. This is because of the intimate relation between the olfactory, trigeminal, and gustatory systems[19,27,28]. It could also be due to the damage of the nasal epithelium and its feeding blood vessels by viral infection.

APPLIED TREATMENT POTENTIALS FOR PERSISTENT POST-COVID-19 SMELL AND TASTE DISORDERS

Smell and taste disorders have important impacts not only at the physical level but also at the emotional and psychological wellbeing level. Smell is important for detection and discrimination of odors, enjoyment of the energizing aroma, judging the qualitative value of odors (pleasant or unpleasant), influencing social behaviors (*e.g.*, social interaction as feelings of attraction or disgust), evoking good memories, and warning against toxins, leaking gas, polluted air, smoke, *etc.* Taste and flavor are important for food choice, enjoyment of the depth and complexity of food and drinks, the general appetite and control of food intake, and the onset of satiation and warn against rotten or toxic foods and drinks.

Post-COVID-19 persistent smell and taste disorders affect the individual not only at the physical but also at the psychological level and can have an impact on the quality of life. Affected patients are often distressed as these impairments can hinder the enjoyment of food and create hygiene problems. Studies from Europe and Asia reported the adverse impact of long-lasting smell disorders on quality of life, personal-social functioning, and mental health. In a cross-sectional study by Bagheri *et al*[124] on 10069 participants responding to an online checklist that evaluated the sense of smell and taste, the results indicated a significant correlation between anosmia caused by SARS-CoV-2 infection, decreased taste sensation, and decreased quality of life.

Trials to treat persistent disorders include the following pharmacotherapies and interventions which are used in routine clinical practice to treat similar disorders from other etiologies[125,126], and they include: Topical intranasal or systemic steroids[126,127], trace elements (*e.g.*, zinc and selenium)[128,129], vitamins [*e.g.*, vitamin B complex (*e.g.*, B1, B2, B6, B9, and B12), vitamin D, vitamin C, and vitamin E][130,131], herbals and other nutritional supplements (*e.g.*, omega-3, L-carnitine[131,132], and alpha-lipoic acid[133]), and olfactory and gustatory training[134].

Zinc is widely used by otolaryngologists to treat smell and taste disorders. Zinc has a role in antiviral immune responses[135,136]. Zinc supplementation has shown efficacy to improve taste disorders which may or may not be accompanied by acute hypozincemia[137]. Zinc also has been shown to inhibit coronavirus RNA polymerase activity *in vitro*[138]. The idea of using B vitamins [thiamine (B1), pyridoxine (B6), and cobalamin (B12)] is based on the fact that these vitamins have neurotropic properties. They can greatly help in improving injured nervous system from different etiologies. They support the development of the new nervous system cells, maintain neuronal viability, and protect nerves against damaging environmental factors. Vitamin B1 facilitates the use of carbohydrates for energy production and acts as a site-directed antioxidant. Vitamin B6 balances nerve metabolism. Vitamin B12 promotes nerve cell survival and maintains myelin sheath and remyelination. Vitamin D, vitamin C, and vitamin E enhance host immunity and have antioxidant properties[139]. Omega-3 contains both docosahexaenoic acid and eicosapentaenoic acid. Omega-3 fatty acid deficient mice demonstrate evidence of olfactory dysfunction and mice receiving omega-3 fatty acids have improved recovery after peripheral nerve injury, which has been linked to neuroprotective effects mediated through antioxidant and anti-inflammatory pathways. Omega-3 also improves immunity and enhances energy production in different tissues[132]. L-carnitine transports long-chain fatty acids into the mitochondria to be oxidized for energy production[131]. A recent study showed that the loss of mitochondrial membrane potential could be related to long-lasting smell loss after SARS-CoV-2 infection[140]. These findings suggest that interventions using antioxidants and microelements conducted early in the course of the disease (including neuroprotectors), along with olfactory training, could be options for treating post-COVID-19 anosmia. Pentoxifylline is a hemorrheologic agent which improves peripheral microvascular blood flow and causes vasodilatation of peripheral blood vessels and could be an option for treating post-COVID-19 anosmia[141].

Olfactory training has been shown to be effective to regain smell loss from different causes; however, its results vary between subjects but generally slow, occurring over months to years. The idea of olfactory training is to strengthen the olfactory nerves by routine smelling. Training often involves daily sniffing of four strong scents (such as lemon, rosemary, curry powder, lavender, pungent herbs, spices cloves, rose, and essential oils containing scents) at least twice a day, as follows: The patient has to choose one scent and smell it for 15-20 s and try to remember what it smelled like if the patient has complete smell loss, then takes a rest for 10 s, followed by smelling the next scent for 15-20 s, then rest for 10 s, and so on until all four scents have been sampled. After 3 mo, the patient has to switch to a new set of four scents and train with them as described before. For parosmia, scent training can also be used, which involves inhaling a particular scent and thinking about what that scent should smell like[134]. For gustatory training, trials include the following: (1) When eating, if the patient cannot taste the full range of flavors of a dish, he/she has to pay attention to the basic five tastants: Sweet, bitter, sour, salty, or umami, as well as to the food's texture and the sensation which is felt in the palate. This will help to focus on what still can be tasted, rather than on what the subject cannot taste; and (2) The patient has to choose meals with a variety of colors and textures using aromatic herbs and spices and to add substances of stronger flavors to the food, such as aged cheese, olive oil, and toasted nuts[134].

None of the above mentioned treatments or interventions provided significant efficacy and the treatment of persistent smell and taste disorders is still a medical challenge. An increasing number of registered trials have been emerged; however, only two were completed and showed that the use of steroids had no therapeutic efficacy[126].

CONCLUSION

The patterns of acute manifestations and the course of smell and taste disorders caused by SARS-CoV-2 infection indicate that there are different proportions of damage of the olfactory epithelial cells by viral infection. Therefore, it is impossible to predict the long-term functional outcome in patients infected with SARS-CoV-2 after the acute deficits. SARS-CoV-2 infects and damages the non-neuronal olfactory

epithelial cells which are important for the health of the OSNs. SARS-CoV-2 causes chemosensory neuronal degeneration, delayed or lack of regeneration, and molecular changes in the host genomic architecture resulting in reduced expression of olfactory sensory receptors. Therefore, the neurogenesis after viral pathology and axonal outgrowth, connections, and re-wiring and the role of neurotrophic factors to restore the olfactory function after SARS-CoV-2 infection are important topics for further investigations. Further experimental studies are also required to determine the cellular and molecular mechanisms of post-COVID-19 taste disorders as they are much understudied compared to smell disorders. There is also a need for studies to determine the different phenotypes and the extent of smell and taste disorders with different mutated SARS-CoV-2 viral infections and the prevalence of persistent smell and taste disorders due to SARS-CoV-2 variant forms (*i.e.*, wild type alpha or delta, omicron, *etc.*). The treatment of persistent smell disorders is still a challenge. None of pharmacotherapies and interventions which were used to treat similar disorders from other etiologies showed any beneficial effect. To my knowledge, there are currently 13 registered trials as shown in the web [WHO International Clinical Trials Registry Platform (ICTRP Search Portal-WHO; https://trialsearch.who.int/), Cochrane ENT Trials Register (https://ent.cochrane.org), Ovid Embase (https://tools.ovid.com), ClinicalTrials.gov, MediFind (https://medifind.in)] including the use of the following: Local steroids; Systemic steroids; Omega 3; Quadruple; Intranasal insulin; Intranasal zinc; Intranasal gabapentin; Ice cube stimulation; Aerosolized retinoic acid; Intranasal theophylline; A combination of oral vitamin A and intense aromatic chemosensory smell training by pulse aromatic stimulation; Platelet-rich plasma isolated from a patient's own blood and intramuscular cerebrolycin, a multimodal neurotropic factor. However, results were "Recruiting" or "Not started recruiting yet" or "Pending" except for two completed trials for the use of steroids but their results showed no efficacy. Further understanding of the unforeseen mechanisms of these disorders may provide insights for beneficial therapies.

FOOTNOTES

Author contributions: Hamed SA was the guarantor and designed the study, did information collection, designed the figures, did manuscript drafting, and revised the article critically for important intellectual content.

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