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Anosmia and Ageusia as Initial or Unique Symptoms after SARS-COV-2 Virus Infection

(Review article)

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ABSTRACT

SARS-CoV-2 (CoV-2) is a coronavirus which is causing the actual COVID-19 pandemic. The disease caused by 2019 new coronavirus (2019-nCoV) was named coronavirus disease-19 (COVID-19) by the World Health Organization in February 2020. Primary non-specific reported symptoms of 2019-nCoV infection at the prodromal phase

are malaise, fever, and dry cough. The most commonly reported signs and symptoms are fever (98%), cough (76%), dyspnea (55%), and myalgia or fatigue (44%). Nonetheless, recent reports suggest an association between COVID-19 and altered olfactory and taste functions, although smell seems to be more affected than taste. These associations of smell and taste dysfunctions and CoV-2 are consistent with case reports describing a patient with SARS with long term anosmia after recovery from respiratory distress, with the observation that olfactory function is commonly altered after infection with endemic coronaviruses, and with data demonstrating that intentional experimental infection of humans with CoV-299 raises the thresholds at which odors can be detected. Post-viral anosmia and is one of the leading causes of loss of sense of smell in adults, accounting for up to 40% cases of anosmia. Viruses that give rise to the common cold are well known to cause post-infectious loss, and over 200 different viruses are known to cause upper respiratory tract infections. I reviewed the possible mechanisms of smell and taste loss in COVID-19. I concluded that since the existence of such a relationship is likely, it is highly recommended that those patients who experience complications such as smell and/or taste loss, even as unique symptoms, should be considered as potential SARS-CoV-2 virus carriers.

SARS-CoV-2 (CoV-2) is a coronavirus which is causing the COVID-19 pandemic.¹⁻⁵ The disease caused by 2019 new coronavirus (2019-nCoV) was named coronavirus disease-19 (COVID-19) by the World Health Organization in February 2020.⁶⁻¹⁰

The 2019-nCoV is phylogenetically related to severe acute respiratory syndrome-coronavirus (SARS-CoV).^{1, 11, 12} It has been shown that 2019-nCoV enters the cell through the ACE2 cell receptor in the same way as the severe acute respiratory syndrome (SARS)

coronavirus. 2019-nCoV effectively uses angiotensin converting enzyme 2 receptor (ACE2) as a receptor for cell invasion.¹³⁻¹⁹

The current knowledge on SARS-CoV-2 is relative scarce, and most of it comes from deductions than actual data analysis.^{3, 20-23} Coronaviruses are known as enveloped viruses with a positive-sense single-stranded RNA genome, and their helical symmetry nucleocapsid is about 26–32 kilobases in size, making it the largest investigated genome among RNA viruses.²³⁻²⁵ SARS-CoV-2 is a betacoronavirus belonging to the 2B group.²⁶⁻³⁰ It shares around 70-80% of its genome with SARS-CoV virus, but it shows to have the uppermost level of likeness with a horseshoe bat coronavirus.^{2, 31-33} Therefore, it is considered to be a recombinant virus transmitted from bats to human hosts by the mean of an intermediate host.^{34, 35} Being an RNA-virus with an RNA-dependent RNA polymerase (RNP)-based replication, mutation and recombination are frequent events. Moreover, in spite of the name and genetic similarities, SARS-CoV-2 shows genetic and clinical differences with SARS-CoV.³⁶⁻⁴⁰

Initial reports stated that primary non-specific reported symptoms of 2019-nCoV infection at the prodromal phase are malaise, fever, and dry cough. The most frequently described signs and symptoms are fever (98%), cough (76%), dyspnea (55%), and myalgia or fatigue (44%).^{5, 41-46}

Nonetheless, recent reports suggest an association between COVID-19 and altered olfactory and taste functions, although smell seems to be more affected than taste.⁴⁷ These associations of smell and taste dysfunctions and CoV-2 are reliable with case reports relating a patient with SARS with long term anosmia after recovery from respiratory distress, with the observation that olfactory function is usually altered after infection with endemic coronaviruses, and with data indicating that deliberate experimental infection of humans with CoV-2 raises the thresholds at which smells can be sensed.⁴⁸⁻⁵² A highly

published news on this issue came when National Basketball Association player Rudy Gobert trapped the coronavirus, and complained loss of smell and taste.⁵¹

Post-viral anosmia and is one of the leading causes of loss of sense of smell in adults, accounting for up to 40% cases of anosmia. Viruses responsible of the common cold are well known to cause post-infectious loss of smell, and over 200 different viruses are known to cause upper respiratory tract infections. Previously descriptions of coronaviruses are supposed to account for 10- 15% cases.²⁶Hence, it is therefore conceivably to suppose that the novel SARS-CoV-2 virus would also cause anosmia in infected patients.⁵²

Anosmia

Anosmia is the loss of the capability to detect one or more smells. Anosmia may be temporary or permanent. Full anosmia is reasonably rare related to hyposmia (a partial loss of smell), and dysosmia (a distortion or alteration of smell). Anosmia has different etiologies, such as inflammation of the nasal mucosa, blockage of nasal passages or a destruction of one temporal lobe. Inflammation is due to chronic mucosa changes in the lining of the paranasal sinus and in the middle and superior turbinates.^{47, 52-61}

Ageusia

Ageusia is the loss of taste functions of the tongue, principally the incapability to sense sweetness, sourness, bitterness, saltiness, and umami, which means pleasant/savory taste. Ageusia is frequently confused with anosmia because the tongue can only indicate texture and distinguish between sweet, sour, bitter, salty, and umami, most of what is perceived as the sense of taste is certainly derivative from smell. Full ageusia is comparatively rare related to hypogeusia (a partial loss of taste), and dysgeusia (a distortion or alteration of

taste). The foremost causes of taste disorders are head trauma, infections of upper respiratory tract, exposure to toxic substances, iatrogenic causes, medicines, and glossodynia (burning mouth syndrome). Head trauma can cause lesions in regions of the central nervous system (CNS) involved in processing taste stimuli, including thalamus, brain stem, and temporal lobes; it can also cause injury to neurological pathways involved in transmission of taste stimuli.^{52, 56, 59-63}

Nervous pathways of smell

The pathway of olfactory conduction begins with the olfactory receptors, which are small, slender nerve cells embedded in large numbers (about 100 million in the rabbit) in the epithelium of the mucous membrane lining the upper part of the nasal cavity. Each olfactory receptor cell emits two processes (projections). One of these is a short peripheral dendrite, which spreads to the surface of the epithelium, where it ends in a knob carrying a number of fine radially placed filaments, the olfactory hairs. The other process is a long and extremely thin axon, the olfactory nerve fiber, which reaches the cranial cavity by passing through one of the foramina in the bony roof of the nasal cavity and arrives the olfactory bulb of the forebrain. Sensations of smell are experienced when certain chemical substances become dissolved in the thin layer of fluid covering the surface of the mucous membrane and then come in contact with the olfactory hairs. The receptor cells differ among themselves in their sensitivities to various odorous substances.⁶⁴⁻⁷⁴

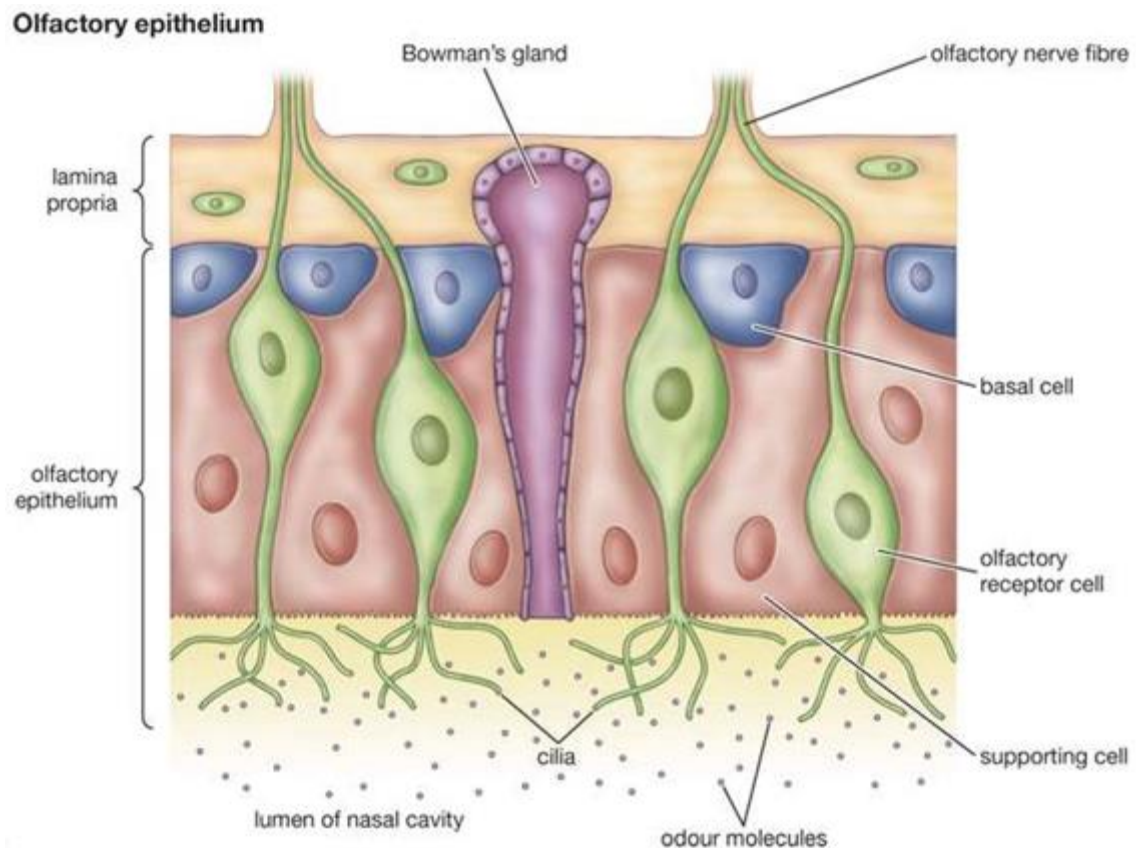


Figure 1. Smell mechanisms. Olfactory epithelium

The olfactory epithelium, found within the nasal cavity, contains olfactory receptor cells, which have specialized cilia extensions. The cilia trap odor molecules as they pass across the epithelial surface. Information about the molecules is then transmitted from the receptors to the olfactory bulb in the brain. In the olfactory bulb, the olfactory nerve fibers end in contact with the antenna-shaped dendrites of the large mitral cells, which represent the second main link in the chain of olfactory conduction. Each mitral cell emits a long axon, many of which enter into the formation of the olfactory tract, a white fiber band extending back from the bulb over the basal surface of the forebrain. The olfactory tract distributes its fibers mainly to the cortex of the pyriform lobe, which constitutes the final cortical receiving area of the olfactory pathway. In humans this region corresponds to the uncus of the hippocampal gyrus. A smaller number of fibers of the olfactory tract end in

two further olfactory structures; the olfactory tubercle and the medial part of the amygdaloid complex (the latter lies deep to the olfactory cortex). In the nasal passage lies the olfactory epithelium (mucous membrane) lined by olfactory receptors. These olfactory receptors contain Golf protein, which are stimulated by odor molecules. Upon stimulation, the Golf protein stimulates the release of a cyclic AMP catalyzing enzyme. When catalyzed, this cyclic AMP serves as a transmitter that signals the opening of sodium ion channels, leading to depolarization of the receptor cells.^{53, 71, 75-79}

Olfactory sensory input travels from the axons through the cribiform plate holes and mitral cell synapses. These mitral cells, found in the olfactory bulbs, comprise the olfactory tract. The information travels through the olfactory tract towards the primary olfactory cortex in the limbic system. This cortex transfers the information to three areas: the hypothalamus, the thalamus and the orbitofrontal cortex. The reception of olfactory input in the orbitofrontal cortex explains why we may perceive smell and taste at the same time.^{71, 75, 80-82}

Taste

The tongue contains small bumps called papillae, within or near which taste buds are situated. In the tongue's taste buds, the taste receptors receive sensory input via two important mechanisms: depolarization and neurotransmitter release. Intake of salty foods leads more sodium ions to enter the receptor, causing the said mechanisms. The same is true with intake of sour foods (hydrogen ions) and sweet foods (sugar molecules), both of which result to the closing of K⁺ channels upon their entry. From the axons of the taste receptors, the sensory information is transferred to the three taste pathways via the branches of cranial nerves VII, IX and X. The chorda tympani of CN VII (facial nerve) carries the taste sensory input from the tongue's anterior two-thirds. Then, the rest of the

taste sensations from the throat, palate and posterior tongue are transmitted by the branches of CN IX (glossopharyngeal nerve) and CN X (vagus nerve). From these cranial nerves, taste sensory input travels through the nerve fiber synapses to the solitary tract, the ventral posteromedial thalamic nuclei, and the thalamus. In these three locations, there are clustered neurons which respond to the same taste (sweet, sour, salty or bitter). The thalamus relays the information to the primary gustatory cortex located in the somatosensory cortex. The primary gustatory cortex is where the perception of a particular taste is processed.^{64, 66, 71, 76, 83-92}

Diagnosis of smell and taste loss

Anosmia can be diagnosed by doctors by using acetylcysteine tests. Doctors will begin with a detailed clinical history about particularities of smell and taste loss. Then the doctor will ask for any related injuries in relation to anosmia which could include upper respiratory infections or head injury.

Ageusia is assessed by measuring the lowest concentration of a taste quality that the subject can detect or recognize. The subject is also asked to compare the tastes of different substances or to note how the intensity of a taste grows when a substance's concentration is increased. Scientists have developed taste testing in which the patient responds to different chemical concentrations. This may involve a simple “sip, spit, and rinse” test, or chemicals may be applied directly to specific areas of the tongue.^{26, 55, 68, 78, 93-104}

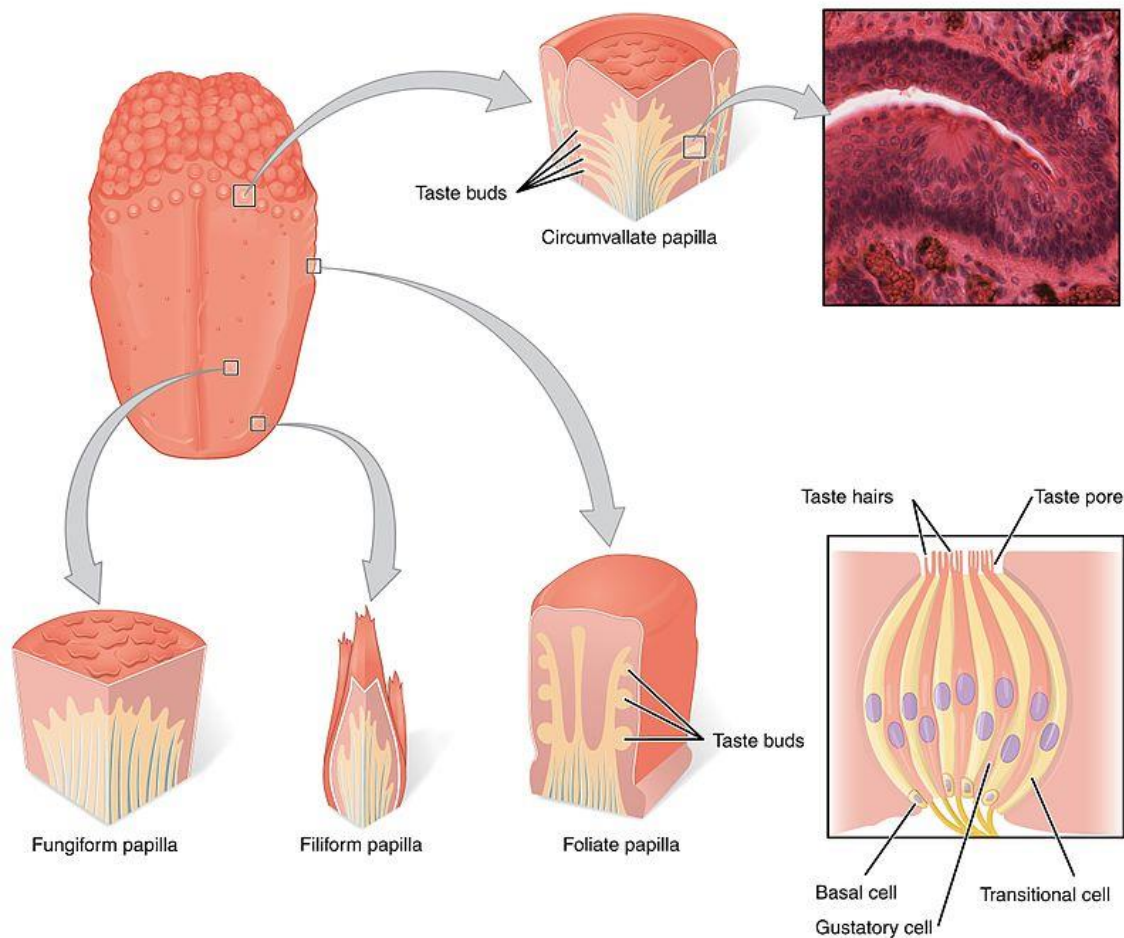


Figure 2. Taste mechanisms. Taste buds and papillae of the tongue

Mechanisms leading to smell and taste sense loss by SARS-Cov-2

Smell loss can be caused by many things, including swelling in the nose and sinuses (such as chronic sinusitis), head injury, and nerve disorders (such as Parkinson's disease). In some cases, no cause is found. The olfactory system is part of the upper respiratory tract in mammals and therefore, pathogens can reach other parts of the respiratory system once they effectively invade the olfactory mucosa. Known respiratory pathogens which infect the human olfactory organ include influenza virus, respiratory syncytial virus, rhinovirus, *Staphylococcus aureus*, *S. pneumoniae*. The upper respiratory system is also connected to the gastrointestinal tract via the esophagus and therefore it is possible for pathogens that cause gastric infection can produce nasal diseases. Although this route is

less well studied, some examples may include human bocavirus, human rotavirus, Epstein-Barr virus and Salmonella enterica.^{26, 50, 105, 106}

Loss of smell because of a viral infection, such as the common cold, is the second most common cause of smell loss and accounts for about 12% of all cases of anosmia. These episodes typically happen when the virus infects the nose, giving rise to the usual cold symptoms, including a blocked or runny nose. Sense of smell usually recovers once symptoms diminish. But sometimes even when other symptoms disappear, sense of smell doesn't subside, or in some cases it's reduced (hyposmia), or is distorted (parosmia).

In these cases, the virus has damaged the smell receptors causing them to lose the fine, hair-like endings that allow them to pick up smell molecules from the nasal mucus. Preceding studies have looked at which viruses cause this condition, and many have been implicated, with the coronavirus family of which COVID-19 is a member.^{26, 49, 50, 52, 105, 106}

The anatomical organization of the human olfactory system makes it an attractive site for pathogens to get into the host. The olfactory system is directly connected to the CNS via the olfactory bulb and consequently frequent neurotropic agents including parasites, bacteria and viruses can reach the CNS via transport lengthways to the olfactory nerve.^{54, 71, 75, 76, 107-110}

Several reports have evaluated coronavirus's effects on the CNS. These studies suggest that the human CNS may be vulnerable to coronavirus infection. The routes for CNS infection with coronaviruses are peripheral trigeminal or olfactory nerves following intranasal inoculation. Studies on rodents demonstrate that these viruses cause demyelination and stimulate T cell-mediated autoimmune reactions against CNS antigens. This fact has raised the question about the relationship between coronaviruses, particularly the 2019-nCoV, and neurologic disorder in humans. Considering that the

peripheral trigeminal or olfactory nerves are pathways of penetration of the coronaviruses into the CNS, and based on animal studies, it may be theorized that complications, such as demyelination and stimulation of T cell-mediated autoimmune reactions, may happen in the path of the infection dispersion, so the incidence of dyssomnia and dysgeusia can be painstaking potential consequences of these nerve injuries.^{26, 49-52, 105, 106}

A virus typically arrives the body by imbedding itself and infecting host cells thru the body, such as in the airways or the gut, and then replicating. During the acute phase of a viral cold a patient may experience nasal congestion and blockage caused by nasal obstruction, membrane edema and excess nasal secretions. This congestion may cause momentary loss of smell and taste but with recovery from the cold, over time, these nasal symptoms vanish, ease of nasal breathing is recommenced and smell and taste function usually recur as they did prior to the onset of the viral cold.^{26, 50, 103, 105, 106, 111-113}

SARS-CoV-2 is believed to enter the nasal and mouth tissues through the angiotensin converting enzyme 2 (ACE2) receptor, although more research is needed to approve whether this is the case. This protein is copious in the nose, although its function is not clear. By entering the nose and mouth through this protein, it may cause temporary damage to the smell and taste nerves. However, this damage appears to get better within one to two weeks after the onset of the disease.^{13-15, 17, 19} Stem cells have probably a role on smell and taste recovering.⁴⁹

It has been hypothesized that a viral replication process is present in the protein secreting glands in the nose and the mouth which is sustained by a dynamic process involving nonstop rounds of de novo virus infection and replication. Hence, the initial systemic viral infection the viral RNA arrives into specific protein secreting glands in the nose and mouth, replicating their genomes. These are usually single stranded RNAs which may produce viral factories that can direct the products of proteins and construction

of new viral particles which can infect these glands. Whereas the systemic viral infection is eliminated this local process can endure to generate viral RNA, which is toxic to the protein secretions generated by these protein secreting glands. This toxicity can constrain secretion of some of the endogenously secreted proteins, so-called growth factors, produced by these glands. These endogenous proteins consist of multiple chemical moieties including cAMP, cGMP and sonic hedgehog. Stem cells, which maintain the receptors of both olfactory epithelial cells for smell and taste bud receptor cells for taste, necessitate continual stimulation by these secreted proteins for these receptors to function. As these receptors turnover as rapidly as every 24 hours, inhibition of these secretions inhibits receptor growth causing loss of smell and taste.^{24, 49, 52, 55, 114-118}

Reports in both mouse and human datasets demonstrate that olfactory sensory neurons do not express two key genes involved in CoV-2 entry, ACE2 and TMPRSS2. In contrast, olfactory epithelial support cells and stem cells express both of these genes, as do cells in the nasal respiratory epithelium. These findings suggest possible mechanisms through which CoV-2 infection could lead to anosmia or other forms of olfactory dysfunction.^{14, 15, 17, 19, 49, 52}

CONCLUSION

Although definitive reports of pervasive CoV-2-associated anosmia have not yet been finally proved, these findings raise the question of how CoV-2 might affect processing mechanisms to change smell and taste perception in COVID-19 patients.^{26, 49, 48, 50-52}

Since the existence of such a relationship is likely, it also seems likely that during the COVID-2019 outbreak, those who experience complications such as smell and/or taste

loss, even as unique symptoms, should be considered as potential SARS-CoV-2 virus carriers.

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