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ENTANGLEMENT OF COVID-19 IN OLFACTORY AND GUSTATORY SYSTEM AND ITS PROGNOSIS

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ABSTRACT

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is spreading rapidly around the world. Early fever, cough (dryness) and fatigue were considered common and most important symptoms of coronavirus-2 infection. However, as the pandemic spread, olfactory and taste dysfunction emerged as a new symptom of COVID-19. This review describes the anatomy and physiology of the olfactory and gustatory area, and the mechanisms affected by COVID-19 that cause olfactory and taste loss i.e. anosmia and ageusia, respectively. The current understanding of pathophysiological mechanisms infers ACE2 (Angiotensin Converting Enzyme 2) and TMPRSS2 (encoded serine protease) expression patterns. Co-expression of ACE2 and TMPRSS2 indicates that olfactory epithelium-supported cells may be the first target for SARS-CoV-2. Direct attack of SARS-CoV-2 on the tongue results in altered stem cell characteristics due to local inflammatory processes, ultimately altering taste. ACE2 is widespread in oral mucosal epithelial cells and, when destroyed, causes ageusia in the early stages of COVID-19. The early prognosis of COVID-19 through olfactory and taste dysfunction can be concluded.

KEYWORDS: *SARS-CoV-2, Chemo sensation, Anosmia, Ageusia, Prognosis.*

INTRODUCTION

The novel coronavirus (COVID-19) was first identified in Wuhan, Hubei province, China on Dec. 31, 2019., in association with a severe human respiratory disease. It has been spread rapidly throughout world after confirmed cases reported by WHO. Authors have reported increase in patients with anosmia, with Mao et al initially reporting on this finding in February 2020. Since then many anecdotal reports have described new-onset of olfactory or gustatory dysfunction along with well-established symptoms of COVID-19 infection, as well as in patients with known positive diagnosis of COVID-19 by laboratory testing. Due to increasing awareness of olfactory or gustatory dysfunction as potential early symptoms of COVID-19 infection, the centres for Disease Control and Prevention (CDC) added "new loss of taste and smell" to its list of symptoms that may appear 2-14 days after exposure to COVID-19. Further on 26th March 2020 to facilitate confidential reporting of olfactory dysfunction along with COVID-19, the American Academy of Otolaryngology – Head & Neck Surgery (AAO-HNS) released the COVID-19 Anosmia Reporting tool. Preliminary review of first 237 submissions to this platform showed that anosmia was present in 73% of cases prior laboratory diagnosis of COVID-19 and presenting symptoms in 26.6%.[1]

The coronavirus family consist of pandemic viruses and endemic viruses. MERS-CoV, SARS-CoV and SARS-CoV-2 are pandemic coronaviruses and HCoV-OC43, HCoV-HKU1, HCoV-229E and HCoVNL63 are endemic coronaviruses. The endemic coronaviruses are associated with both acute and chronic changes in smell and taste. It infects the upper airway and causes frequent common cold. The changes in acute viral mediated infection includes conductive deficits by loss of patency caused by swelling of the mucosa and increased mucus production, changes in mucus composition and secondary changes include olfactory signaling due to local release of inflammatory intermediates like cytokines. Currently, the limited data suggests that parosmia are infrequent during or after COVID-19 recovery.[2]

Problems in smell and taste have come up as the predominant neurological symptom of the coronavirus disease (COVID-19), which is caused by SARS-CoV-2.

Around 80% or more patients infected with SARS-CoV-2 reported anosmia, hyposmia, ageusia, dysgeusia or changes in chemesthesis.[3]

Self-reported changes in smell and taste functions can predict whether a subject will test positive for SARS-CoV-2. Recently, a study was carried out which included more than 2 million participants revealed that loss of smell and taste is more predictive than all other symptoms (Manni et al., 2020). Due to this, researchers are trying to develop accessible smell and taste in which individuals rate the quality and intensity of scents originating from, e.g., scratch and sniff cards or common kitchen items for potential use as screening tools for COVID-19 (Iravani et al., 2020). Loss of smell and taste in COVID-19 infection forces us to investigate that how SARS-CoV-2 might alter the cells and circuits charged with detecting stimuli and creating perception. If we identify these pathophysiological mechanisms, it may help for treatment method selection, as well as for designing clinical chemosensory assessment to detect SARS-CoV infection.[4]

Here, we will be mainly focusing on interactions between 1) SARS-CoV-2 and olfactory system 2) SARS-CoV-2 and gustatory system, which have been explored till now as much pandemic has progressed.

Olfactory system

Olfactory conduction begins with the Olfactory receptors. They are embedded in large numbers in the epithelium of the mucous membrane lining the upper part of the nasal cavity. Each olfactory receptor cell emits two processes. One is the short peripheral dendrites and the other is the olfactory nerve fibers, which are long and very thin axons. The short peripheral dendrites reach the surface of the epithelium and end with knobs that carry the olfactory hairs. The olfactory nerve fibers pass through one of the nasal bone roof openings to reach the cranial cavity and enter the olfactory bulb of the forebrain. The sensation of odor occurs when certain chemicals dissolve in a thin layer of liquid that covers the surface of the mucous membrane, thereby contacting the olfactory hair. Perhaps it will be found that the receptor cells differ among them in their susceptibility to various odorants.[5]

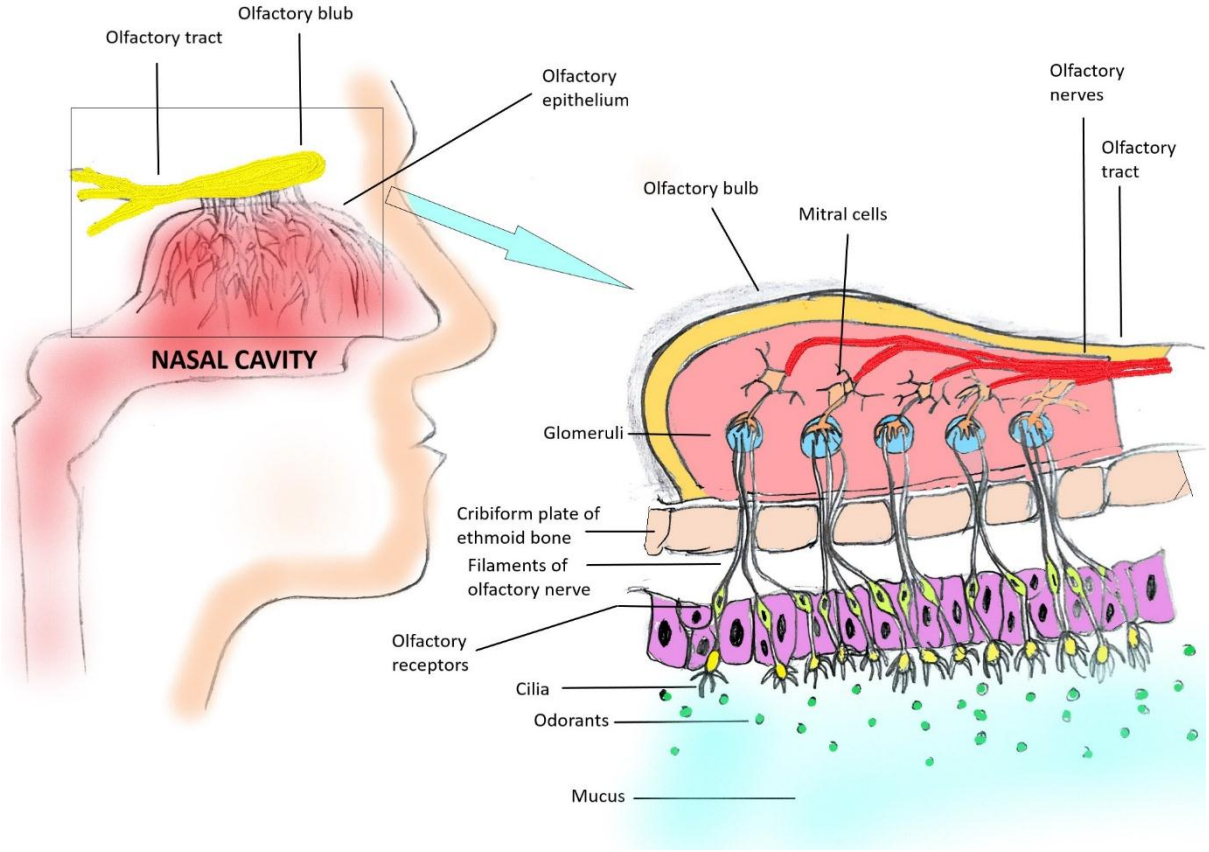

Figure 1: Olfactory system.

In the olfactory bulb, olfactory nerve fibers end in contact with the antenna-shaped dendrites of large mitral cells, which represent the second major link in the olfactory conduction chain. Each mitral cell releases long axons, many of which enter the formation of the olfactory tract. The olfactory tract distributes its fibers primarily to the cortex and constitutes the final cortical receptive region of the olfactory pathway. In highly developed olfactory mammals such as rodents, the structure of the olfactory brain is relatively large and occupies all or most of the basal surface of the forebrain. Significant reductions in all olfactory structures are

evident in primates (monkeys, apes, and humans), whose orientation is highly dependent on sight and touch. In recent studies the COVID-19 patients suffer anosmia due to inflammation of olfactory epithelium and olfactory bulb.[5]

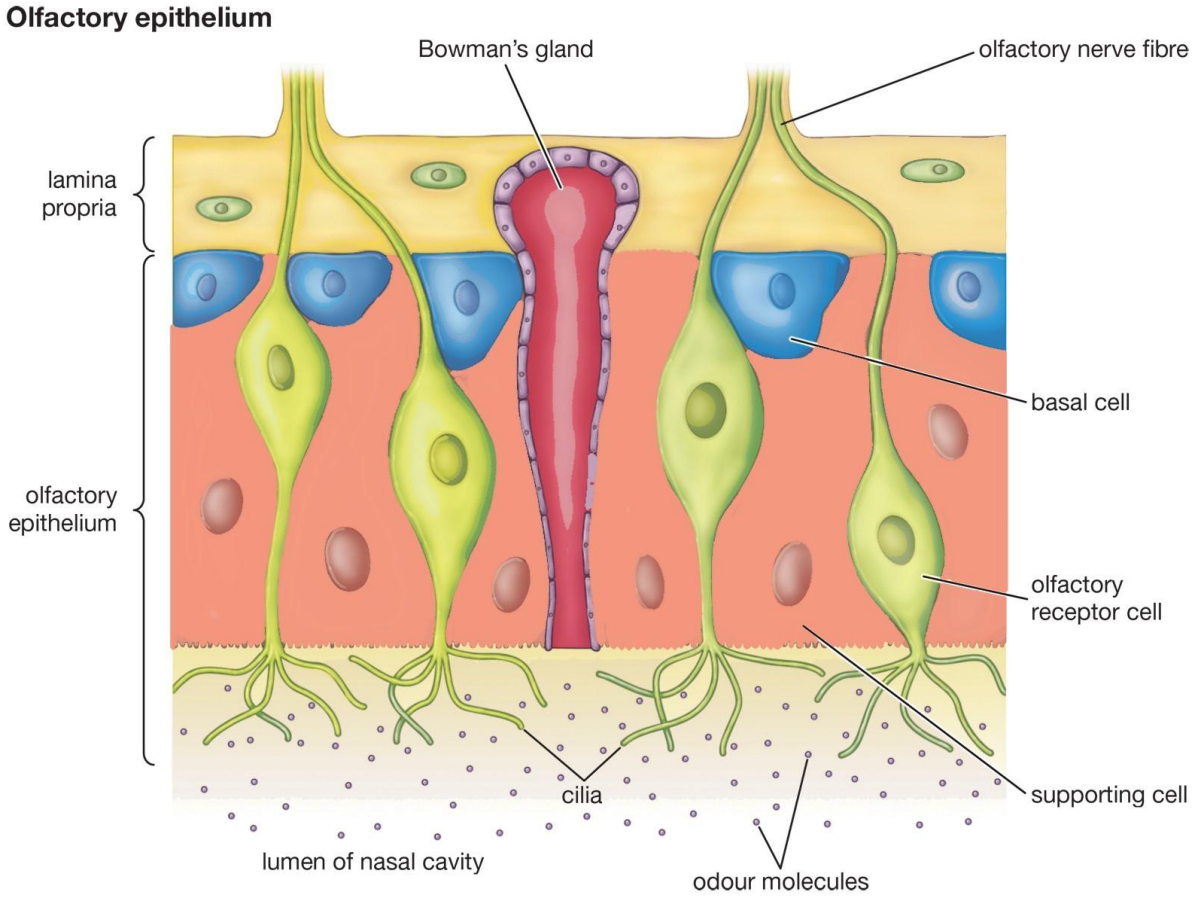

Figure 2: Olfactory Epithelium.[5]

Because of the halo of spike (S) proteins on their surface the virus is named as coronavirus.[6,7] These S proteins interact with specific cellular receptors to bind host cells; binding is followed by protease-mediated S protein cleavage, which exposes fusion-promoting domains that enable viral entry.[2] The SARS-CoV-2 infects the cells through interactions between the S proteins and Angiotensin Converting Enzyme 2 (ACE2) receptor on the target cells. ACE2 modulates the Renin Angiotensin system (regulation of blood pressure and salt water balance).[8,9,10] Infection to occur S protein cleavage is required. Cleavage can occur via host cell serine protease TMPRSS2 and by other proteases.[11,12]

The endemic coronavirus HCoV-NL63 is an exception who does not use ACE2 as its primary target.[13,14] The difference between SARS-CoV and SARS-CoV-2 is their binding to ACE2 receptor considering chemosensory modalities (olfaction and gustatory functions).[15,16] The SARS-CoV-2 spike protein binds ACE2 with higher affinity and with a different binding mode than that of SARS-CoV. Although SARS-CoV-2 can enter the epithelium cells by directly binding to angiotensin converting cell surface[17] enzyme 2 (ACE2) protein, olfaction receptor cells do not express ACE2 or other cells, unlike the genes involved in SARS-CoV-2 entry (TMPRSS2) epithelial persistence and stem cells. Olfactory receptor neurons may initiate a rapid immune response in the host with the manifestation of olfactory dysfunction.[18] Therefore, the olfactory receptor uptake of SARS-CoV-2 into other cells important for sustainability olfactory receptor cell population.

Table 1: Types of Smell Dysfunction.

Anosmia	Loss of smell
Hyposmia	Reduced ability to smell and detect odor
Chemesthesis	Ability to sense chemical irritants

As, SARS-CoV-2 attacks the olfactory system and thus, many patients report anosmia as their first symptom. Indeed, the sensitivity of anosmia increases in patients without other nasal symptoms. Some studies reported

that cells in the nasal respiratory epithelium (RE) have higher expression of SARS-CoV-2 entry genes than cells in the RE that line the trachea or lungs.[19,20] Recent studies also reported that nasal epithelium is also a major source of viral RNA after SARS-CoV-2 in several species, like cats, ferrets, and monkeys.[21,22] Thus, it can be concluded that nasal epithelium act as a major reservoir for the coronaviruses.

Chemo sensation takes place in sensory epithelia in both nose and mouth. In nose the odor detection occurs via olfactory epithelium (OE) and olfactory bulb (OB). The olfactory sensory neurons (OSNs) which resides in olfactory epithelium are responsible for airborne odors. Their axons further pierce the cribriform plate and enters the olfactory bulb in the brain.[2] In some patients, viral infections lead to direct damage to OSNs which can causes long lasting post viral anosmia.[23] Recruitment of stem cells in OE which can replace damaged OSNs can cause partial or full recovery of olfactory functions in these patients.[2] Whereas in some patients it is been hypothesized that post viral anosmia can cause viral damage to central nervous system via OB through OSNs or by indirectly passing through the cribriform plate by perforations.[24,25]

The OE is composed of multiple cell types, including immature and mature OSNs, non-neuronal cell types such as the sustentacular, Bowman's gland, and microvillar cells, and stem cells including globose and horizontal basal cells. Sustentacular cells are associated with OSNs, and they wrap the sensory dendritic cilia which are present in airspace and enable odor detection.[26] Some recent studies reported that OSNs does not express ACE2. But there are co-expressions of ACE2 and TMPRSS2, which was observed in key support cells (including sustentacular, Bowman's gland, and microvillar cells) and stem cells that can replace the epithelium after damage.[27,28,29] Thus, the co-expressions of ACE2 and TMPRSS2 indicate that the OE support cells can be the initial targets of SARS-CoV-2.

Olfactory clefts comprise of 5% of the total nasal epithelium. It is a pair of narrow passages in the superior region of nasal epithelium through which air must flow to reach the OE. Local inflammation may block the olfactory clefts.[30,31] A recent study revealed blockage of olfactory cleft in COVID-19 patient. The localized inflammation might increase the inflammatory intermediates like cytokines.[32] The studies suggested that these inflammatory intermediates may indirectly lower the expression of Odor Receptor (OR) which could cause changes in odor perception.[33]

SARS-CoV-2 infection affects the support cells. Example, Bowman's glands secrete mucus which is essential for normal odor perception.[34,35,36] Sustentacular cells and microvillar maintain local salt and water. The Sustentacular cells also support the OSN sensory cilia. Increased damage to these support cells, OSNs and OE may conclude long lasting anosmia in COVID-19 patients.[37] The horizontal basal cells that has major role in regenerating the OE, also expresses the ACE2.[27,37] Thus, infection of the cells may lead to slow recovery of odor perception.

Recent studies reported that transient changes were observed in OB in covid-19 patients. Some of the coronaviruses can infect the OB via passage through OE.[38,39] But it remains unclear for SARS-CoV 2 that it could not directly infect the OSNs and thus cannot pass the olfactory nerve. However, single cell RNA Sequencing(scSeq) and immunostaining of the mouse OB has revealed that bulb neurons of nose do not express detectable levels of ACE2.[27] Whereas pericytes in the OB express high levels of ACE2 protein. The expression of ACE2 protein is also reported in perivascular cells in the brain and throughout the body.[2] Pericytes have a critical role in maintaining the Blood Brain Barrier. Thus, infection of these cells can indirectly affect the neurons involved in odor perception in brain.[40] With recent observations in the OB, there is an increasing amount of data suggesting that ACE2 is not appreciably expressed in neurons in the brain at either the RNA or protein level.[27] Infection of macaques, cats, and ferrets with SARS-CoV-2 (which in the monkey and cat resulted in pulmonary infection) did not reveal any virus present in the brain.[21,22] In addition, recent human autopsy studies reveal that the brain contains the least amount of SARS-CoV-2 of any sampled tissue in the body.[42]

Gustatory system

The taste buds are found in fungiform papillae (FFP) at the front of the tongue. FFP is distributed in the anterior lingual epithelium, which is covered by mechanosensory filiform papillae (flp). In the posterior tongue, large complex papillae (circumvallate [CVP] and foliate [FolP]) are epithelial invaginations containing hundreds of buds each; rodents have a single CVP, whereas humans have a single 8-12 CVP's in an inverted V arrangement across the posterior tongue.[42] Each bud is a collection of 100 taste receptor cells (TRC) classified into three types based on morphology (I for support or glial-like, II for sweet, bitter, umami, and III for sour).

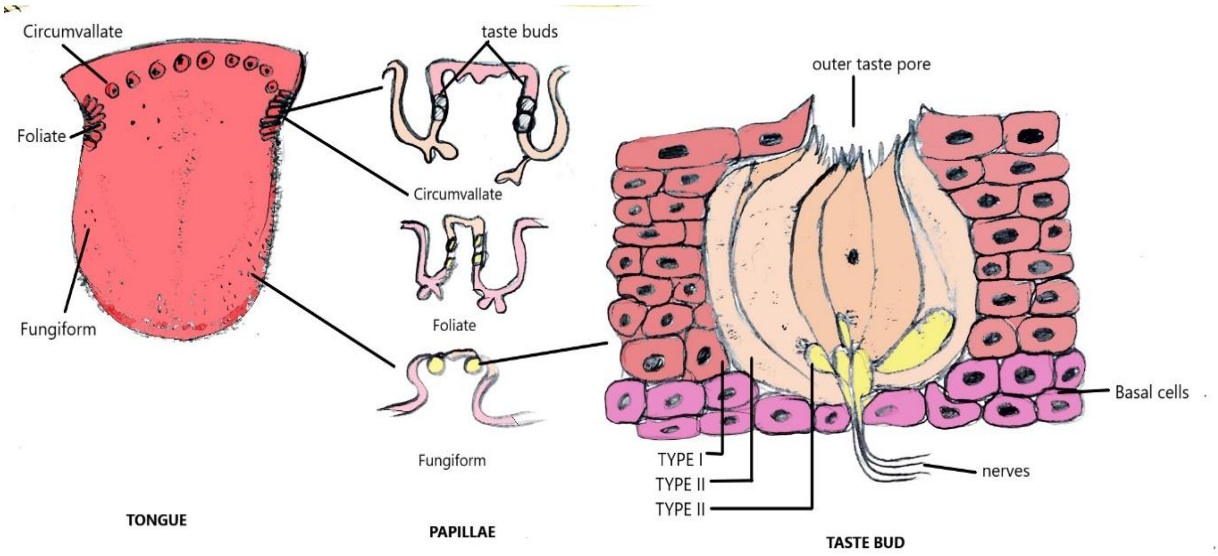

Figure 3: Gustatory system.

From basal stem cells adjacent to taste bud (Basal Cell), all TRCs are continually renewed. The taste function and perception therefore it also relies on the rapid and reliable development of the appropriate proparts of each of the different TRCs.[43,44,45] Publicly accessible data sets of Type II and Type III TRC in mice show that ACE2 is expressed through Sour sensing Type III TRCs, and to a lesser degree through bitter and sweet / umami sensing Type II TRCs.[46,47,48,49] While type II and type III TRCs express little to no TMPRSS2, Cathepsin (Cathepsin B (CTSB) and Cathepsin L (CTSL)) are abundant and may act as proteases to cleave SARS-CoV-2 spike protein at type II and type III TRCs. Available data sets do not include transcriptional profiling for the type I TRCs, which much like olfactory sustentacular cells extend cellular processes that wrap type II and type III TRCs.[26,51] Type I cells often degrade ATP, which is used by type II cells as neurotransmitter to relay taste informative to the brain via the gustatory nerves.[52,53,54] If type I cells are ACE 2 positive and SARS-CoV-2 targeted, the loss of support cells might lead to the collapse of taste buds via cell death and/or decreased efficacy of taste signals to the gustatory nerves. Adult taste stem cells (where they are most abundant) in the posterior tongue express the marker LGR5 (Leucine-rich repeat-containing G-protein coupled receptor 5) and can give rise to all TRC lineage.[55] Despite the small sample size, scSeq profiling has shown that murine LGR5 positive stem cells express ACE2 and TMPRSS2 and may therefore be competent for SARS-CoV-2 infection.[48] These data give rise to the possibility of a taste dysfunction in COVID-19 patients may be caused or exacerbated by insufficient TRC renewal due to SARS-CoV-2 stem cell damage. In addition, experimentally induced systemic inflammation in mice has been shown to decrease the production of taste stem cells, which depopulated taste buds and disrupted taste function. Therefore, if SARS-CoV- 2 infects the tongue directly, local inflammatory processes might alter the properties of stem cells and ultimately affect the perception of taste.[56,57,58,59,60] In line with this possibility, scSeq research in mice and humans indicates that ACE2 is highly expressed in subgroups of tongue epithelial cells, as are other coronavirus related proteases, such as TMPRSS11D, TMPRSS4, and CTSB.[61,62,63,64] As with the Type I TRCs, whether SCCs (solitary chemosensory cells) express SARS-CoV-2 cell entry genes is not yet clear from sequencing results. Therefore, it remains unclear how SARS-CoV-2 affects chemesthesis, although these effects are unlikely to be mediated by trigeminal neurons not expressing ACE2 or TMPRSS2.[65,66]

The sensation of flavour consists of the compounds inclu ding the odor's smell, taste, temperature, and texture. Ea ch of these sensory compounds is stimulated separately t o create a unique flavour when we take a meal. The over all prevalence of gustatory dysfunction is less often than that of olfactory dysfunction. The ability to distinguish flavours is dependent on the pathway of retro nasal stimulation. Therefore, retro nasal olfactory deficiency is usually referred to as "loss of taste" patients. However, some studies have identified a high expression of ACE2 in the mucosa of the oral cavity and tongue epithelial cells. Simply put, another possibility is that SARS-COV-2 will directly affect buds of receptors.[64,67]

Ageusia may be due to olfactory deficiency as a secondar y outcome. The angiotensin converting enzyme 2 receptor, which is the primary SARS-CoV-2 host cell receptor for binding and penetrating cells, is however widely expressed in oral mucosal epithelial cells.[64]

Table 2: Definition of taste disorders.[68]

Disorders of detection	
Normogeusia	Normal taste function
Hypogeusia	Quantitatively reduced taste function
Ageusia	Absence of all taste function
Disorders of identification(dysgeusia)	
Parageusia	Altered taste perception (an unpleasant taste) with external stimulus present
Phantogeusia	Perception of metallic or salty taste without external stimulus present

Disruption to oral cavity mucosal epithelial cells can explain ageusia seen at the early stage of COVID-19. Gustatory conditions recorded by Lechien JR et al[69] were as large as 88.8 percent (308 of 342), consisting of 78.9 percent hypogeusia / ageusia and 21.1 percent parage-usia. There was a substantial link between smell and taste disorders. Yan CH. et a.[70] recorded that 71% (42 of 59) of COVID-19 patients had gustatory dysfunction; some patients displayed signs of acute ageusia without any odour dysfunction. Interestingly, it was not what we expected that prevalence of gustatory dysfunction would be higher than smell dysfunction in almost all studies.[71,72,73] Of the 1390 COVID-19 patients registered some degree of gustatory dysfunction was observed in 626 patients in the 9 trials. The prevalence reported by individual studies of gustatory dysfunction ranged from 5.61 percent to 92.65 percent. A 43.93 percent prevalence of gustatory dysfunction (95 percent CI, 20.46 percent- 68.95 percent) was demonstrated by metanalysis using a random effects model. In the COVID-19 Anosmia Reporting Method, Kaye et al[74] did not distinguish between olfactory and gustatory dysfunction, instead considering gustatory dysfunction because of olfactory dysfunction.

In a reported measure of combined "chemosensory dysfunction'', Vaira et al[75] attempted to capture gustatory dysfunction. All other research included in this study attempted to distinguish gustatory dysfunction and all 8 of these research documented gustatory disturbance in COVID-19 patients. Only Lechien et al[69] used a validated measure to evaluate the taste portion of the NHANES[76] for gustatory dysfunction. Given the well-established effect on the sensory experience of taste[77] of olfactory stimuli gustatory dysfunction may also be an early symptom indicative of COVID-19 infection, although this symptom appears to have been examined less robustly. Consequently, it remains unclear if gustatory dysfunction is a distinct clinical manifestation of the virus, or if this occurs secondary to olfactory dysfunction. Beltra 'nCorbellini et al[78] recorded that the initial symptom was olfactory or gustatory dysfunction in 35.5 per cent of COVID-19 patients, with an acute onset in 70.9 percent of COVID-19 patients with olfactory or gustatory dysfunction included in the study. From 72 COVID-19 patients' study in University of Hospital of Cologne, Germany reduced olfaction resulted in 53 COVID-19 patients (74 percent) while reduced a sense of taste was present in 50 COVID-19 patients (69 percent). 49 patients (68%) registered all symptoms,while one pati ent (1%) had a reduced sense of taste only, and four patie nts (6%) had a reduced sense of smell only. Both sympto ms emerged on average at the fourth day after the first sy -mptoms had been reported. However, nine patients (13%) noticed that reduced olfaction and loss of sense occurred together on the first day they realized any symptoms. One patient had reduced sense of taste alone at the first day he realized any symptoms.

According to the paper from USA reported that 68% and 71% of 59 patients had olfactory and gustatory dysfunction, respectively. According to the larger-scale research from Europe, 85.6% of the 417 mild-to-moderate COVID-19 patients had olfactory dysfunctions and 88.8% gustatory dysfunctions. Only 5.1% of 214 patients complained of hyposmia and 5.6% hypogeusia in China. However, it has been documented that 33.9% of 59 COVID-19 patients in Italy complained of olfactory and/or gustatory dysfunction and 11% complained of both dysfunctions, it has been documented.

In Spain 31.65% and 35.44% of 79 COVID-19 patients complained olfactory and gustatory dysfunction. From USA paper it was reported that 68% and 71% of 59 patients had olfactory and gustatory dysfunction. In China only 5.6% of 214 complained about hypogeusia. From different papers it shows the rate of olfactory or gustatory dysfunction is supposed to be different between Europe/USA, and China (or Asia).[80] In a questionnaire-based, cross-sectional study conducted in Italy of 88 hospitalised COVID-19 patients, 59 patients were able to be interviewed include gustatory manifestations of dysgeusia (5 patients; 8.5%) and ageusia (1 patient; 1.7%). Furthermore, 78.9% and 21.1% patients reported reduced/discontinued or distorted abilities to taste flavours, respectively.[81]

PROGNOSIS

Data in Europe shows a 44 percent recovery rate (72.6 pe rcent recovered within the first eight days).[70] Similarly, in the other study in the US, 74 percent of affected patien ts, both olfactory and taste, reported improvement, associ ated with total resolution of clinical symptoms.

Currently, the rate of restoration of short-term smell and taste is between 44-74 percent, which is greater than prior studies of other post viral olfactory dysfunction such as rhinovirus, measles, syncytial respiratory virus, and other coronaviruses. It is, however, much too early

to determine long-term olfactory changes in COVID-19 patients and gustatory changes.[68] The median time to recovery from anosmia and ageusia was 7 days, and the recovery time pattern is depicted in Fig. 4A and Fig. 4B, respectively.

Most anosmia or ageusia patients recovered within 3 wee ks. Recovery from ageusia was like that from anosmia. Young age, particularly the age group of 20–39 years, showed a tendency to be associated with a longer persistence of anosmia.[82]

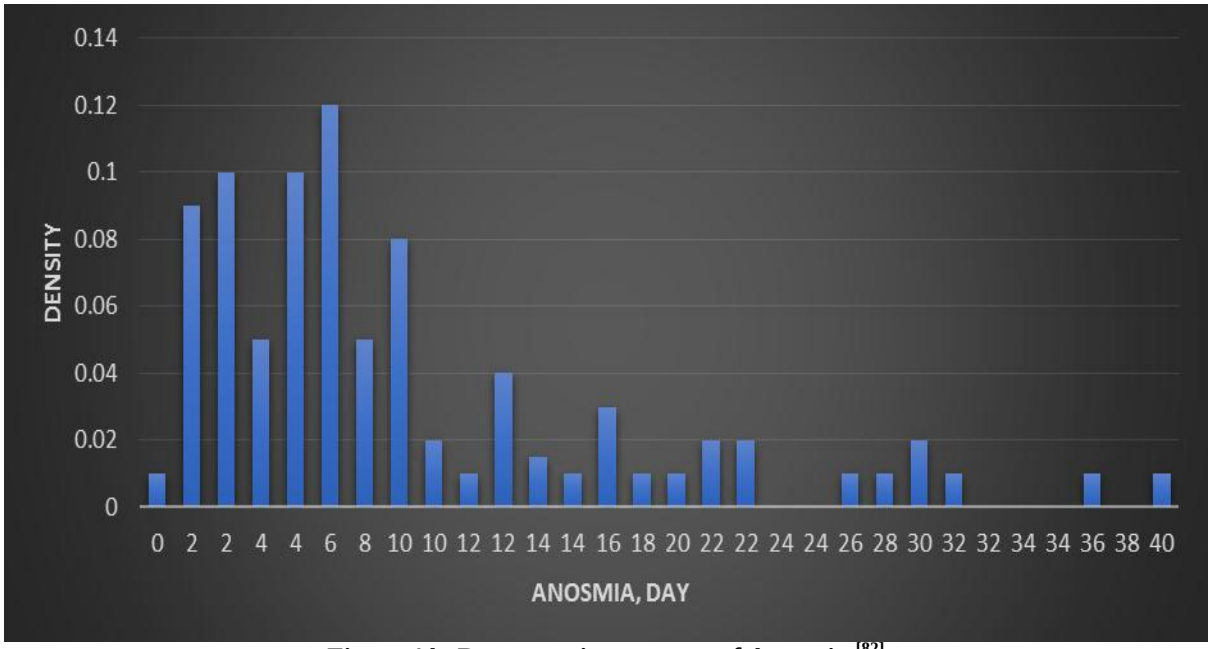

Figure 4A: Recovery time pattern of Anosmia.[82]

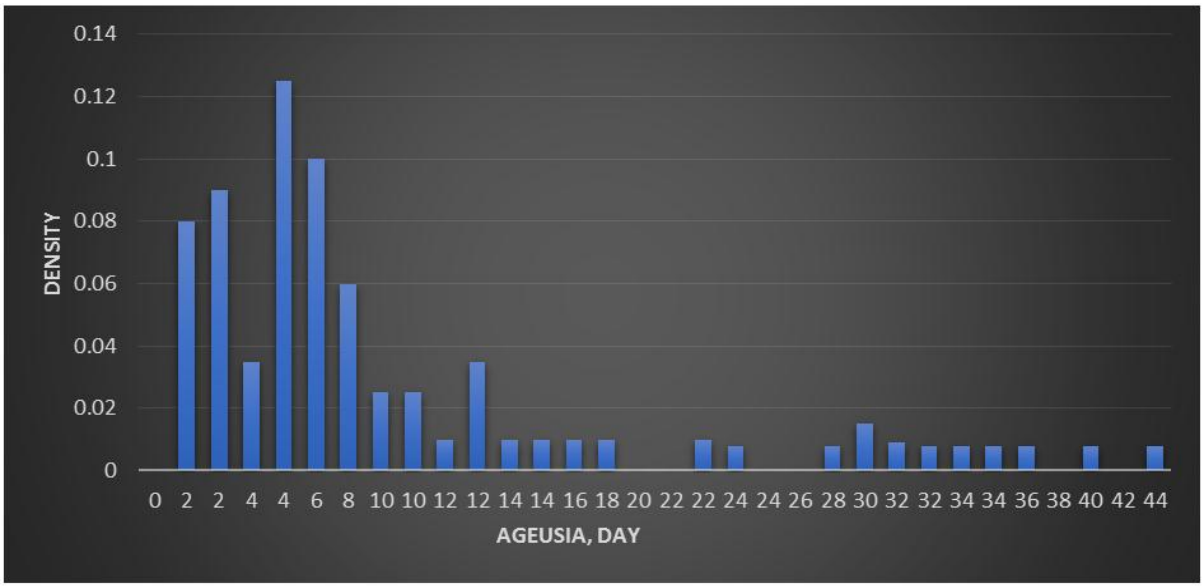

Figure 4B: Recovery time pattern of Ageusia.[82]

CONCLUSION

Around the globe, the number of COVID-19 patients is growing. Due to the increasing reported pieces of evidence from several countries latest reports now support that unexpected olfactory or gustatory impairment may be a presenting symptom of SARS-CoV-2 infection. Analysis into potential pathways that underlie chemical perception changes due to COVID-19 has only just started, and much needs to be known about SARS-CoV-2 pathophysiology. It is still uncertain whether COVID-19 attacks chemo sensation by one or more pathophysiological pathways, due to the variety of symptoms documented by patients. From existing evidence that favours the model in which SARS-CoV-2 cell entry genes are not expressed in primary or secondary neurons in the olfactory, gustatory, and chemesthesis systems, but are expressed in epithelial, support, and stem cells responsible for maintaining perception.

ACE2 is mandatory for SARS-CoV-2 entry, high low-level expression of ACE2 may be sufficient to promote SARS-CoV-2 infection, meaning that SARS-CoV-2 may apparently infect ACE2-negative cell types. The ACE2 gene is controlled by inflammation in human cells, and primary infection and inflammation may also modulate other SARS-CoV-2 entry genes. This finding raises the probability of a larger cells producing ACE2 during SARS-CoV-2 than is generally appreciated.

Smell and taste recovery predictions for SARS-CoV-2 are higher than for other post-viral infections. And within 3 weeks, these symptoms may heal. Anosmia and ageusia are very relevant indicators of early COVID-19 identification and may be beneficial for immediate diagnosis and treatment. It could also be helpful for patient self-isolation, potentially facilitating the breakup of this viral outbreak.

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REFERENCES

1. Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T.The Prevalence of Olfactory and Gustatory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis. Otolaryngol Head Neck Surg, 2020; 163(1): 3-11.
2. Keiland W. Cooper, David H. Brann, Michael C. Farruggia, Surabhi Bhutani, Robert Pellegrino, Tatsuya Tsukahara, Caleb Weinreb, Paule V. Joseph, Eric D. Larson, Valentina Parma, Mark W. Albers, Linda A. Barlow, Sandeep Robert Datta, AntonellaDi Pizio. COVID-19 and the Chemical Senses: Supporting Players Take Center Stage. Neuron, 2020; 107(2): 219-233.
3. Yun Jin Kang, JinHee Cho, Min Hyeong Lee, Yeon Ji Kim, Chan-Soon Park. The diagnostic value of detecting sudden smell loss among asymptomatic COVID-19 patients in early stage: The possible early sign of COVID-19. Auris Nasus Larynx, 2020; 47(4): 565-573.
4. Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. Int Forum Allergy Rhinol, 2020; (8): 944-950.
5. By courtesy of Encyclopaedia Britannica, Inc.https://www.britannica.com/science/olfactory-system/Nervous-pathways-of-smell
6. Du, L., He, Y., Zhou, Y. et al. The spike protein of SARS-CoV — a target for vaccine and therapeutic development. Nat Rev Microbiol, 2009; 7: 226–236.
7. Perlman, S., Netland, J. Coronaviruses post-SARS: update on replication and pathogenesis. Nat Rev Microbiol, 2009; 7: 439–450.
8. Shang, J., Ye, G., Shi, K. et al. Structural basis of receptor recognition by SARS-CoV-2. Nature, 2020; 581: 221–224.
9. Alexandra C. Walls, Young-Jun Park, M. Alejandra Tortorici, Abigail Wall, Andrew T. McGuire, David Veesler, Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell, 2020; 181(2): 281-292.
10. Zhou, P., Yang, X., Wang, X. et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature, 2020; 579: 270–273.
11. Markus Hoffmann, Hannah Kleine-Weber, Stefan Pöhlmann. A Multibasic Cleavage Site in the Spike Protein of SARS-CoV-2 Is Essential for Infection of Human Lung Cells. Mol. Cell, 2020; 78(4): 779-784.
12. Zang R, Gomez Castro MF, McCune BT, Zeng Q, Rothlauf PW, Sonnek NM, Liu Z, Brulois KF, Wang X, Greenberg HB, Diamond MS, Ciorba MA, Whelan SPJ, Ding S. TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes. Sci Immunol, 2020; 5(47): 3582.
13. Belouzard, S.; Millet, J.K.; Licitra, B.N.; Whittaker, G.R. Mechanisms of Coronavirus Cell Entry Mediated by the Viral Spike Protein. Virus, 2012; 4: 1011-1033.
14. Zumla, A., Chan, J., Azhar, E. et al. Coronaviruses — drug discovery and therapeutic options. Nat Rev Drug Discov, 2016; 15: 327–347.
15. Li, W., Moore, M., Vasilieva, N. et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature, 2003; 426: 450–454.
16. Jian Shang, Yushun Wan, Chuming Luo, Gang Ye, Qibin Geng, Ashley Auerb ach, Fang Li. Cell entry mechanisms of SARS-CoV-2. Proc. Natl. Acad. Sci. U.S.A, 2020; 117(21): 11727-11734.
17. Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. Biochem Biophys Res Commun, 2020; 526(1): 135-140.
18. Butowt R, Bilinska K. SARS-CoV-2: Olfaction, Brain Infection, and the Urgent Need for Clinical Samples Allowing Earlier Virus Detection. ACS Chem Neurosci, 2020; 11(9): 1200-1203.
19. Hou, Y.J., Okuda, K., Edwards, C.E., Martinez, D.R., Asakura, T., Dinnon, K.H., 3rd, Kato, T., Lee, R.E., Yount, B.L., Mascenik, T.M., et al. SARS-CoV-2 Reverse Genetics Reveals a Variable Infection Gradient in the Respiratory Tract. Mol. Cell, 2020; 182: 1–18.
20. Sungnak, W., Huang, N., Bécavin, C. et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med, 2020; 26: 681–687.
21. Munster, V.J., Feldmann, F., Williamson, B.N. et al. Respiratory disease in rhesus macaques inoculated with SARS-CoV-2. Nature, 2020; 585: 268–272.

22. Shi, J., Wen, Z., Zhong, G., Yang, H., Wang, C., Huang, B., Liu, R., He, X., Shuai, L., Sun, Z., et al. Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2. Science, 2020; 368: 1016–1020.
23. Cavazzana, A., Larsson, M., M€unch, M., H€ahner, A., and Hummel, T. Postinfectious olfactory loss: A retrospective study on 791 patients. Laryngoscope, 2018; 128: 10–15.
24. van Riel, D., Verdijk, R., and Kuiken, T. The olfactory nerve: a shortcut for influenza and other viral diseases into the central nervous system. J. Pathol, 2015; 235: 277–287.
25. Barnett, E.M., and Perlman, S. The olfactory nerve and not the trigeminal nerve is the major site of CNS entry for mouse hepatitis virus, strain JHM. Virol.J, 1993; 194: 185–191.
26. Liang, F. Sustentacular Cell Enwrapment of Olfactory Receptor Neuronal Dendrites: An Update. Genes, 2020; 11: 493.
27. Brann, D., Tsukahara, T., Weinreb, C., Lipovsek, M., Van den Berge, K., Gong, B., Chance, R., Macaulay, I.C., Chou, H.-j., Fletcher, R., et al. Nonneuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. bioRxiv, 2020.
28. Chen, M., Shen, W., Rowan, N.R., Kulaga, H., Hillel, A., Ramanathan, M., and Lane, A.P. Elevated ACE2 expression in the olfactory neuroepithelium: implications for anosmia and upper respiratory SARS-CoV-2 entry and replication. bioRxiv, 2020.
29. Fodoulian, L., Tuberosa, J., Rossier, D., Landis, B.N., Carleton, A., and Rodriguez, I. SARS-CoV-2 receptor and entry genes are expressed by sustentacular cells in the human olfactory neuroepithelium. bioRxiv 2020.
30. Besser, G., Liu, D.T., Renner, B., Hummel, T., and Mueller, C.A. Reversible obstruction of the olfactory cleft: impact on olfactory perception and nasal patency. Int. Forum Allergy Rhinol, 2020; 10: 713–718.
31. Trotier, D., Bensimon, J.L., Herman, P., Tran Ba Huy, P., Døving, K.B., and Eloit, C. Inflammatory obstruction of the olfactory clefts and olfactory loss in humans: a new syndrome? Chem. Senses, 2007; 32: 285–292.
32. Eliezer, M., Hautefort, C., Hamel, A.-L., Verillaud, B., Herman, P., Houdart, E.,and Eloit,C. Sudden and Complete Olfactory Loss Function as a Possible Symptom of COVID-19. JAMA Otolaryngol. Head Neck Surg, 2020.
33. Rodriguez, S., Cao, L., Rickenbacher, G.T., Benz, E.G., Magdamo, C., Ramirez Gomez, L.A., Holbrook, E., Dhilla Albers, A., Gallagher, R., Westover, M.B., et al. Innate immune signaling in the olfactory epithelium reduces odorant receptor levels: modeling transient smell loss in COVID-19 patients. medRxiv, 2020.
34. Dear TN, Boehm T, Keverne EB, Rabbitts TH. Novel genes for potential ligand-binding proteins in subregions of the olfactory mucosa. EMBO J, 1991; 10(10): 2813-2819.
35. Kern RC. Chronic sinusitis and anosmia: pathologic changes in the olfactory mucosa. Laryngoscope, 2000; 110(7): 1071-7.
36. Tom T. Solbu, Torgeir Holen, "Aquaporin Pathways and Mucin Secretion of Bowman's Glands Might Protect the Olfactory Mucosa. Chem. Senses, 2012; 37(1): 35–46.
37. Schwob, J.E., Jang, W., Holbrook, E.H., Lin, B., Herrick, D.B., Peterson, J.N., and Hewitt Coleman, J. Stem and progenitor cells of the mammalian olfactory epithelium: Taking poietic license. J. Comp. Neurol, 2017; 525: 1034–1054.
38. Mathieu Dubé, Alain Le Coupanec, Alan H. M. Wong, James M. Rini, Marc Desforges, Pierre J. Talbot. Axonal Transport Enables Neuron-to-Neuron Propagation of Human Coronavirus OC43. J Virol, 2018; 92(17): 00404-18.
39. Durrant, D.M., Ghosh, S., and Klein, R.S. The Olfactory Bulb: An Immunosensory Effector Organ during Neurotropic Viral Infections. ACS Chem. Neurosci, 2016; 7: 464–469.
40. Annika Armulik, GuillemGenové, Christer Betsholtz, Pericytes: Developmental, Physiological, and Pathological Perspectives, Problems, and Promises." Dev Cell, 2011; 21(2): 193-215.
41. Puelles, V.G., L€utgehetmann, M., Lindenmeyer, M.T., Sperhake, J.P., Wong, M.N., Allweiss, L., Chilla, S., Heinemann, A., Wanner, N., Liu, S., et al. Multiorgan and Renal Tropism of SARS-CoV-2. N. Engl. J. Med, 2020.
42. Barlow L. A. Progress and renewal in gustation: new insights into taste bud development. Development, 2015; 142(21): 3620–3629.
43. Gaillard D, Xu M, Liu F, Millar SE, Barlow LA. β-Catenin Signaling Biases Multipotent Lingual Epithelial Progenitors to Differentiate and Acquire Specific Taste Cell Fates. PLoS Genet, 2015; 11(5): 1005208.
44. Liu, H. X., Ermilov, A., Grachtchouk, M., Li, L., Gumucio, D. L., Dlugosz, A. A., & Mistretta, C. M. Multiple signaling centers participate in fungiform papilla and taste bud formation and maintenance. Dev. Biol, 2013; 382(1): 82–97.
45. Okubo, T., Clark, C., & Hogan, B. L. Cell lineage mapping of taste bud cells and keratinocytes in the mouse tongue and soft palate. Stem cells, 2009; 27(2): 442–450.
46. Han, Q.; Peng, J.; Xu, H.; Chen, Q. Taste Cell Is Abundant in the Expression of ACE2 Receptor of 2019-nCoV. Preprints, 2020; 2020040424.
47. Lee H, Macpherson LJ, Parada CA, Zuker CS, Ryba NJP. Rewiring the taste system. Nature 2017; 548(7667): 330-333.
48. Qin Y, Sukumaran SK, Jyotaki M, Redding K, Jiang P, Margolskee RF. Gli3 is a negative regulator of

Tas1r3-expressing taste cells. PLoS Genet, 2018; 14(2): 1007058.
49. Shigemura N, Takai S, Hirose F, Yoshida R, Sanematsu K, Ninomiya Y. Expression of Renin-Angiotensin System Components in the Taste Organ of Mice. Nutrients, 2019; 11(9): 2251.
50. Zhang J, Jin H, Zhang W, Ding C, O'Keeffe S, Ye M, Zuker CS. Sour Sensing from the Tongue to the Brain. Cell, 2019; 179(2): 392-402.
51. Yang R, Dzowo YK, Wilson CE, Russell RL, Kidd GJ, Salcedo E, Lasher RS, Kinnamon JC, Finger TE. Three-dimensional reconstructions of mouse circumvallate taste buds using serial blockface scanning electron microscopy: I. Cell types and the apical region of the taste bud. J Comp Neurol, 2020; 528(5): 756-771.
52. Bartel DL, Sullivan SL, Lavoie EG, Sévigny J, Finger TE. Nucleoside triphosphate diphosphohydrolase-2 is the ecto-ATPase of type I cells in taste buds. J Comp Neurol, 2006; 497(1): 1-12.
53. Finger TE, Danilova V, Barrows J, Bartel DL, Vigers AJ, Stone L, Hellekant G, Kinnamon SC. ATP signaling is crucial for communication from taste buds to gustatory nerves. Science, 2005; 310(5753): 1495-9.
54. Vandenbeuch A, Anderson CB, Parnes J, Enjyoji K, Robson SC, Finger TE, Kinnamon SC. Role of the ectonucleotidase NTPDase2 in taste bud function. Proc Natl Acad Sci U S A, 2013; 110(36): 14789-94.
55. Yee KK, Li Y, Redding KM, Iwatsuki K, Margolskee RF, Jiang P. Lgr5-EGFP marks taste bud stem/progenitor cells in posterior tongue. Stem Cells, 2013; 31(5): 992-1000.
56. Cohn ZJ, Kim A, Huang L, Brand J, Wang H. Lipopolysaccharide-induced inflammation attenuates taste progenitor cell proliferation and shortens the life span of taste bud cells. BMC Neurosci, 2010; 11: 72.
57. Feng P, Huang L, Wang H. Taste bud homeostasis in health, disease, and aging. Chem Senses 2014; 39(1): 3-16.
58. Kaufman A, Choo E, Koh A, Dando R. Inflammation arising from obesity reduces taste bud abundance and inhibits renewal. PLoS Biol, 2018; 16(3): 2001959.
59. Wang H, Zhou M, Brand J, Huang L. Inflammation activates the interferon signaling pathways in taste bud cells. J Neurosci, 2007; 27(40): 10703-13.
60. Wang H, Zhou M, Brand J, Huang L. Inflammation, and taste disorders: mechanisms in taste buds. Ann N Y Acad Sci, 2009; 1170: 596-603.
61. Pisco, A.O., McGeever, A., Schaum, N., Karkanias, J., Neff, N.F., Darmanis, S., Wyss-Coray, T., and Quake, S.R, 2020. A Single Cell Transcriptomic Atlas Characterizes Aging Tissues in the Mouse. bioRxiv.
62. Tabula Muris Consortium; Overall coordination; Logistical coordination; Organ collection and processing; Library preparation and sequencing; Computational data analysis; Cell type annotation; Writing group; Supplemental text writing group; Principal investigators. Single-cell transcriptomics of 20 mouse organs creates a Tabula Muris. Nature, 2018; 562(7727): 367-372.
63. Venkatakrishnan AJ, Puranik A, Anand A, Zemmour D, Yao X, Wu X, Chilaka R, Murakowski DK, Standish K, Raghunathan B, Wagner T, Garcia-Rivera E, Solomon H, Garg A, Barve R, Anyanwu-Ofili A, Khan N, Soundararajan V. Knowledge synthesis of 100 million biomedical documents augments the deep expression profiling of coronavirus receptors. eLife, 2020; 9: 58040.
64. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, Li T, Chen Q. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci, 2020; 12(1): 8.
65. Nguyen MQ, Wu Y, Bonilla LS, von Buchholtz LJ, Ryba NJP. Diversity amongst trigeminal neurons revealed by high throughput single cell sequencing. PLoS One, 2017; 12(9): 0185543.
66. Nguyen MQ, Le Pichon CE, Ryba N. Stereotyped transcriptomic transformation of somatosensory neurons in response to injury. eLife, 2019; 8: 49679.
67. Vaira LA, Salzano G, Fois AG, Piombino P, De Riu G. Potential pathogenesis of ageusia and anosmia in COVID-19 patients. Int Forum Allergy Rhinol, 2020; 10(9): 1103-1104.
68. Kanjanaumporn J, Aeumjaturapat S, Snidvongs K, Seresirikachorn K, Chusakul S. Smell and taste dysfunction in patients with SARS-CoV-2 infection: A review of epidemiology, pathogenesis, prognosis, and treatment options. Asian Pac J Allergy Immunol, 2020; 38(2): 69-77.
69. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol, 2020; 277(8): 2251-2261.
70. Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. Association of chemosensory dysfunction and COVID-19 in patients presenting with influenza-like symptoms. Int Forum Allergy Rhinol, 2020; 10(7): 806-813.
71. Levinson R, Elbaz M, Ben-Ami R, Shasha D, Levinson T, Choshen G, Petrov K, Gadoth A, Paran Y. Time course of anosmia and dysgeusia in patients with mild SARS-CoV-2 infection. Infect Dis, 2020; 52(8): 600-602.
72. Bénézit F, Le Turnier P, Declerck C, Paillé C, Revest M, Dubée V, Tattevin P; RAN COVID Study Group. Utility of hyposmia and hypogeusia for the diagnosis of COVID-19. Lancet Infect Dis, 2020; 20(9): 1014-1015.
73. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, Rusconi S, Gervasoni C, Ridolfo AL, Rizzardini G, Antinori S, Galli M. Self-reported Olfactory and Taste Disorders in Patients With

Severe Acute Respiratory Coronavirus 2 Infection: A Cross-sectional Study. Clin Infect Dis, 2020; 71(15): 889-890.
74. Kaye R, Chang CWD, Kazahaya K, Brereton J, Denneny JC 3rd. COVID-19 Anosmia Reporting Tool: Initial Findings. Otolaryngol Head Neck Surg, 2020; 163(1): 132-134.
75. Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and Ageusia: Common Findings in COVID-19 Patients. Laryngoscope, 2020; 130(7): 1787.
76. Bhattacharyya N, Kepnes LJ. Contemporary assessment of the prevalence of smell and taste problems in adults. Laryngoscope, 2015; 125(5): 1102-6.
77. Djordjevic J, Zatorre RJ, Jones-Gotman M. Effects of perceived and imagined odors on taste detection. Chem Senses, 2004; 29(3): 199-208.
78. Beltrán-Corbellini Á, Chico-García JL, Martínez-Poles J, Rodríguez-Jorge F, Natera-Villalba E, Gómez-Corral J, Gómez-López A, Monreal E, Parra-Díaz P, Cortés-Cuevas JL, Galán JC, Fragola-Arnau C, Porta-Etessam J, Masjuan J, Alonso-Cánovas A. Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicentre polymerase chain reaction based case-control study. Eur J Neurol, 2020; 10: 1111.
79. Luers JC, Rokohl AC, Loreck N, Wawer Matos PA, Augustin M, Dewald F, Klein F, Lehmann C, Heindl LM. Olfactory and Gustatory Dysfunction in Coronavirus Disease 2019 (COVID-19). Clin Infect Dis, 2020; 71(16): 2262-2264.
80. Kang YJ, Cho JH, Lee MH, Kim YJ, Park CS. The diagnostic value of detecting sudden smell loss among asymptomatic COVID-19 patients in early stage: The possible early sign of COVID-19. Auris Nasus Larynx. 2020; 47(4): 565-573.
81. Lai CC, Ko WC, Lee PI, Jean SS, Hsueh PR. Extra-respiratory manifestations of COVID-19. Int J Antimicrob Agents, 2020; 56(2): 106024.
82. Lee Y, Min P, Lee S, Kim SW. Prevalence and Duration of Acute Loss of Smell or Taste in COVID-19 Patients. J Korean Med Sci, 2020; 35(18): 1.