Review of taste and taste disturbance in COVID-19 patients

Guangzhao Guan, Alison Mary Rich, Ajith Polonowita, Li Mei

ABSTRACT

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is responsible for the coronavirus disease 2019 (COVID-19) pandemic that has become a significant global public health concern. The virus gains entry to cells via angiotensin-converting enzyme-2 (ACE2) receptors, which have been found to be the functional receptor for SARS-CoV-2 infection. High expression of ACE2 is found in type II alveolar cells, macrophages, bronchial and tracheal epithelial cells and in the oral cavity, particularly on the tongue. Taste disturbance is one of the early symptoms of COVID-19, suggesting that taste cells in taste buds are vulnerable to SARS-CoV-2 infection. Taste is modulated by hormones that are regulated in the renin-angiotensin-aldosterone system. Hypothetical causes of taste disturbance by SARS-CoV-2 may be due to direct cell and/or neuronal injuries, inflammatory responses and dysregulation of ACE2.

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which was reported by the World Health Organization (WHO) on 31 December 2019. The exact route of transmission is not yet fully solved. It is thought to be via respiratory droplets, similar to the spread of influenza virus. Besides respiratory droplets, SARS-CoV-2 RNA can be found in the blood and stool specimens and have been found to contaminate objects and surfaces such as plastic and stainless steel, copper and cardboard for more than three days.[1,2] Fomite transmission is likely to be a further mode of transmission for SARS-CoV-2.[3] However, vertical transmission (transplacental transmission and breast milk) and faecal–oral (or faecal-aerosol) of SARS-CoV-2 rarely occurs.[4] The spectrum of the illness of COVID-19 ranges from asymptomatic to critical (respiratory failure and/or multiorgan dysfunction); fortunately, most infections are not severe.[5]

How does SARS-CoV-2 enter cells?

Angiotensin-converting enzyme-2 (ACE2) is well known to be the receptor responsible for allowing SARS-CoV-2 to enter cells.[6] Once the viral spike protein binds to ACE2, it is primed by the transmembrane protease serine 2 (TMPRSS2) of host cells, thereby facilitating viral entry. Organs with high numbers of cells expressing ACE2 and TMPRSS2 are considered to be potentially high-risk sites for initial SARS-CoV-2 infection.[7,8] High expression of ACE2 and TMPRSS2 proteins are found in the tongue, hard palate, nose, larynx and hypopharynx, trachea, oesophagus and lung.[8] ACE2 is highly expressed in the oral cavity, with the majority (96%) of the ACE2-positive cells being found in tongue epithelium.[9]

Taste and COVID-19

Patients with COVID-19 have reported lack of taste (ageusia) and decreased taste (hypogeusia) as well as taste disturbance with bitter, sour or metallic sensations on the tongue.[10,11] Reports have confirmed that taste disturbance/loss is an early symptom of subclinical SARS-CoV-2 infection.[10] An Italian cross-section study found that 33.9% patients reported at least one taste or olfactory disorder and 18.6% both.[12] A multi-center European study of 417 hospitalised COVID-19 patients found that 88% of the patients had dysgeusia,[13] and in a group of 59 COVID-19 positive patients in the USA, 71% of patients experienced taste loss.[14]

However, the exact mechanism leading to taste alteration remains unclear.

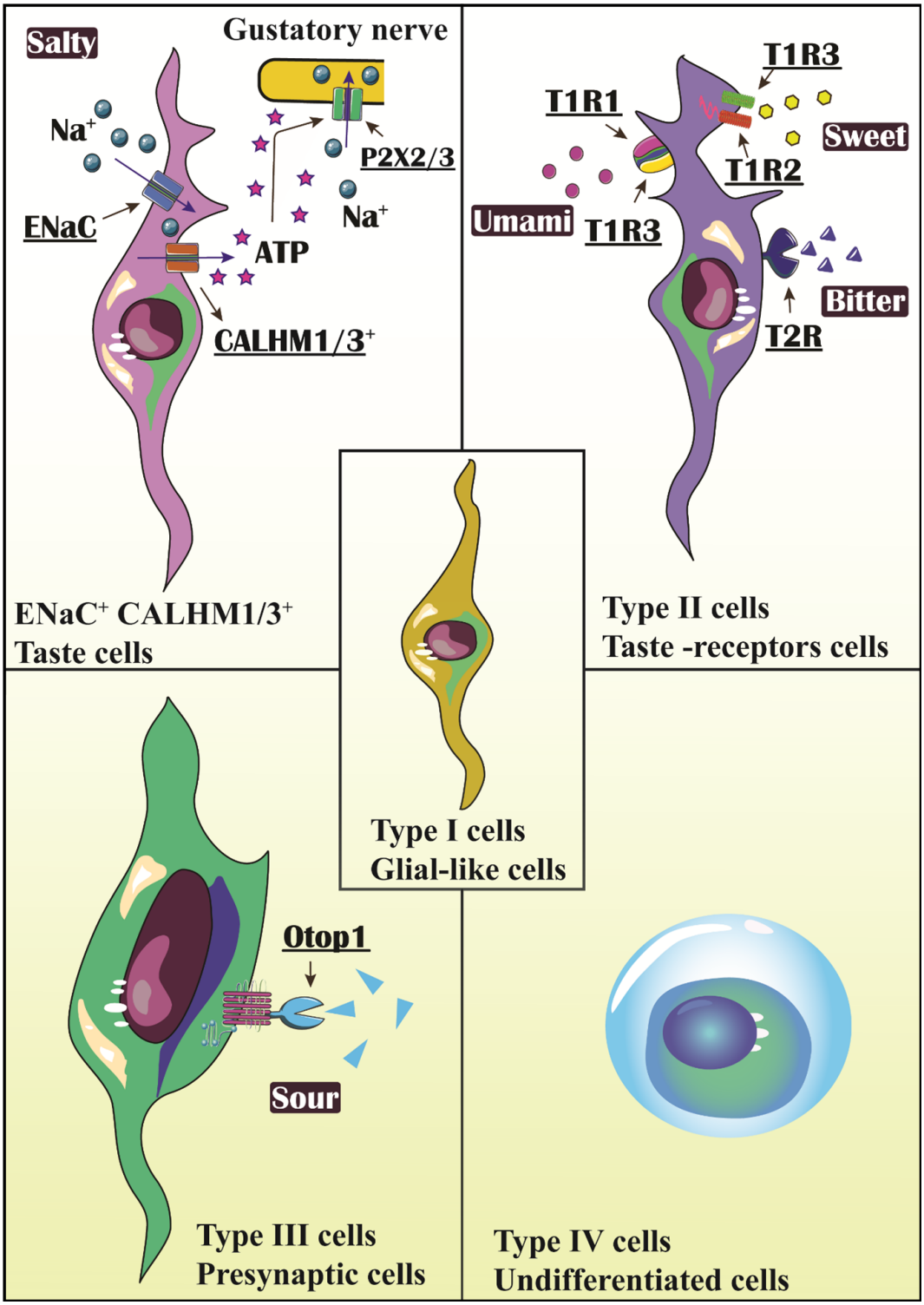
Significant progress has been made to elucidate the cellular and molecular mechanisms of coronavirus-induced taste dysfunction. There are five elements of taste perception: saltiness, sourness, bitterness, sweetness and umaminess. Gustaoception is based on the detection of chemical stimulants by taste buds in the oral cavity. Taste buds are mainly located on the tongue, but they are also found on the soft palate, upper oesophagus and epiglottis. Taste buds are innervated by the seventh, ninth and tenth cranial nerves. There are at least five types of taste cells (Figure 1), with type I cells being the most abundant in taste buds.[15] Salty taste is thought to be mediated by amiloride-sensitive and insensitive receptors on type I cells,[16,17] although others have suggested they provide glial-like support functions and are non-excitable.[18] Type II cells have at least three subsets which respond to sweet, umami and bitter tastants. Type II cells express glial glutamate/aspartate taste receptor type 1 (T1r) and 2 (T2r) on the surface. T1r2 and T1r3 heterodimer is a sweet taste receptor; T1r1 and T1r3 heterodimer is an umami taste receptor; T2r receptor is a bitter taste receptor.[19] Although both T1r and T2r are closely related to the G-protein-coupled pheromone receptors V2R and V1R,[20] T2r genes form a larger multigene family than T1r genes. In contrast to the presence of three T1r genes in the mammalian genome, more than thirty T2r genes exits in human.[21] Type III cells have identifiable synaptic contacts with the gustatory nerves and are believed to express sour taste receptor (The proton-selective ion channel Otop1) on the surface.[22] Type IV cells are the undifferentiated cells at the bottom of the taste bud.[23] A new study has shown that salty taste might be transduced by taste cells that express the amiloride-sensitive epithelial sodium channel/calcium homeostasis modulator 1 and 3 (ENaC+ CALHM1/3+).[24]

Gustatory information from taste receptor cells in the tongue is transmitted to the primary gustatory cortex in the brain via multiple neural stations.[25] Currently, two different models have been suggested to account for the information coding in the gustatory system. One theory, referred to as an "across-fibre pattern recognition," suggests that each chemical has its pathway pattern, and that the information is transmitted by multiple afferent nerves. Therefore, the recognition and classification of the taste are based on these complex patterns across all of the afferent nerve fibres, rather than by activity in any single nerve fibre.[26] The second theory, referred to as "labeled lines," suggests that individual taste receptor cells will respond to only a single taste quality. Each taste quality is transmitted by separate afferent pathways to the gustatory. Experimental results have shown special molecules called "semaphorins" might be responsible for establishing and maintaining appropriate connectivity between taste-receptor cells and their ganglion neurons.[27] These specialised proteins might be involved in maintaining the "labeled lines" between peripheral receptors and their respective central projection area.[26] However, the true mechanism remains unclear, and gustatory information coding may utilise both types of mechanisms.

Renin-Angiotensin-Aldosterone System, COVID-19 and taste

SARS-CoV2 is thought to gain entry into cells by binding to ACE2, a key regulatory enzyme of the angiotensin hormonal system. The Renin-Angiotensin-Aldosterone System (RAAS) is a significant hormone system that regulates blood pressure, fluid and electrolyte homeostasis and systemic vascular resistance. There is growing evidence that taste function is modulated by hormones that govern the RAAS.[28] ACE2 is a key regulatory enzyme that degrades angiotensin II into angiotensin (1–7) and cleaves angiotensin I to angiotensin (1–9). It belongs to the membrane-bound carboxypeptidase family and is widely expressed and distributed in the human body, including in the heart, kidney, ileum and lung.[29] ACE2 has been found to be a functional receptor for SARS-CoV-2 infection and that the virus gains its entry to the cell via this receptor.[30] Extensive expression of ACE2 on the tongue in human was shown in an animal model, where renin, angiotensinogen, ACE1 and ACE2 were present in the taste buds of fungiform

Figure 1: The five different taste cells and their receptors (Adapted from Normura et al.[24]).



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and circumvallate papilla.[31] These results indicate that the tongue, especially the taste buds, may be an important target for SARS-CoV-2 infection. It had been thought that ACE2-positive cells were associated with taste buds,[32] but it has now been found that ACE2 is enriched in the non-gustatory filiform papillae and not in the taste buds. Only a small proportion of type III taste cells of the tongue showed positive expression.[33] Further studies are required to clarify whether ACE2-positive cells are concentrated in taste buds, in filiform papillae or both.

Angiotensin II and aldosterone are the key hormones that regulate sodium and water balance in the taste system. Amiloride is an inhibitor of the epithelial sodium channel, which has been suggested to be one of the sensors of salty taste.[28,34] Mice which lacked epithelial sodium channels on taste cells demonstrated a complete loss of amiloride-sensitive sodium taste responses but retained normal responses to sweet, umami, bitter and sour.[34] Humans do not appear to have a strong amiloride-sensitive salt taste transduction mechanism, when compared with other species.[35] Therefore, amiloride-sensitive channels may play little role in the perception of saltiness in humans. An animal study has shown that administration of aldosterone could increase the amiloride-sensitivity of the rat chorda tympani nerve response to sodium chloride.[36] Aldosterone pre-treatment, a low sodium diet or both could enhance the expression of the epithelial sodium channel in fungiform, foliate and circumvallate taste buds. The total number of amiloride-sensitive cells increased after aldosterone treatment.[37] Such responses are thought to be due to the synthesis and translocation of the epithelial sodium channel from intracellular locations to the apical membrane in the taste cells.[37] Hence aldosterone could enhance amiloride-sensitive salt taste responses.

Angiotensin II is one of the powerful key active products of RAAS and plays an essential role in the regulation of vascular tone, cardiac function and renal sodium reabsorption. Angiotensin II is degraded into angiotensin (1–7) by endopeptidases or carboxypeptidases such as ACE2. Angiotensin II is thought to be a potent stimulator of sodium appetite and preference.[31] Angiotensin II is further converted by aminopeptidase A and aminopeptidase N into other metabolite peptides with different bioactivities. Angiotensin II, the biologically active component of renin-angiotensin system, acts through two receptor subtypes, the AT1 and the AT2 receptors.[38] AT1 receptors are widely distributed throughout the body, including vascular smooth muscle, kidney, heart and brain, and they are responsible for mediating cardiovascular effects such as vasoconstriction, aldosterone synthesis and secretion, and sodium reabsorption. AT2 receptors are thought to have the opposite effect of AT1.[39] In taste buds, AT1 receptors are expressed in some type I and type II taste cells, but not AT2, suggesting that the taste organs may be one of the peripheral targets of angiotensin II.[40] An animal immunohistochemistry study revealed that AT1 receptors were co-expressed with amiloride-sensitive salty receptors, epithelial sodium channels and sweet taste receptors (T1r3).[28] Interestingly, angiotensin II could induce gustatory nerve responses to sweeteners, but not to certain salty substances such as potassium chloride, sour, bitter or umami tastants.[28] These results suggested that angiotensin II not only acts on the taste organ but also modulates the gustatory nerve responses to salty and sweet taste.[40] However, angiotensin II displays an acutely suppressed effect on salty taste while aldosterone acts as a slow enhancer in peripheral taste organs. Concurrently, angiotensin II increases sweet taste sensitivity; hence it may contribute to increased calorie intake.[16]

Hypothetical causes of taste disturbance by SARS-CoV-2

Taste loss associated with impairment of smell

The majority of taste disorders are caused by impairment of smell rather than gustatory loss. However, COVID-associated chemosensory impairment is not limited to smell but also affects taste.[12] Often anosmia and loss of taste are prodromal symptoms when serum cytokine levels are low. A recent European study has shown that anosmia was present in 47% confirmed

COVID-19 patients.[41] It has been reported that smell loss (peak on day three) is earlier than taste loss (peak on days three to seven).[42] A recent study has shown that COVID-19 is associated with olfactory loss but not with gustatory dysfunction when tested.[43] The cause of smell dysfunction in COVID-19 is not fully understood but may be associated with (1) nasal obstruction, congestion and rhinorrhea, (2) death of olfactory receptor neurons, (3) damage of the olfactory centers by viral infiltration and (4) reduction of support cells in the olfactory epithelium.[44]

Direct taste cell damage

Taste buds contains both short-lived and long-lived cell populations.[45] The average turnover rate of taste cells is between eight and twelve days, but some of them (type III cells) can survive longer.[46,47] The homeostasis of taste buds is well maintained across the lifespan. However, disturbances can occur under various pathological conditions. Disruption to taste bud homeostasis, such as abnormal or suboptimal cell turnover, differentiation and degeneration, predisposes to taste disturbance associated with diseases and ageing.[46] Taste disturbance is well known to be related to a wide range of viral infections, including SARS-CoV-2.[14] Hypogeusia and dysgeusia are common complaints of patients with upper respiratory viral infections and oral cavity infections. Similar to respiratory epithelium, both human and animal studies have demonstrated that ACE2, which is used for entry by SARS-CoV-2, is widely expressed in the tongue.[9,31] As a result, the tongue can be a potential target. SARS-CoV-2 is capable of replication in the upper respiratory tissues.[48] Similarly, the destruction of taste cells may be mediated by direct exposure to the virus and active replication of the virus inside the host cells. The damaged taste cells may release more viral particles; as a result, the adjacent taste cells, epithelial cells and neurons could be affected.

Neural injury and taste dysfunction in COVID-19

The maintenance of taste buds is highly dependent on the gustatory nerves.[49,50] Damage to the peripheral or central nervous system can affect the taste. It is known that human coronaviruses may invade the nervous system and cause neurological symptoms.[51] Animal studies revealed that SARS-CoV or Middle East respiratory syndrome coronavirus (MERS-CoV) are capable of causing nerve damage.[52,53] When the virus was given transnasally to mice, it spread further to the brain by damaging olfactory nerves.[53] Several cases of neurological involvement during SARS and MERS, and the potential mechanisms, have already been described in the literature.[51,54] For example, SARS-CoV can induce neurological diseases such as epilepsy, polyneuropathy, olfactory neuropathy, stroke, encephalitis and chronic post-SARS syndrome and autonomic dysfunction.[55] Almost one fifth of MERS-CoV-infected patients developed neurological symptoms during the acute infection.[56] Similar to SARS-CoV, SARS-CoV-2 profits from the ACE2 receptor to enter the intracellular space. Expression of ACE2 receptors has been found in glial cells, neurons, endothelial cells and smooth muscle cells.[55] Therefore, the nervous system can be a potential target of COVID-19. Similar to SARS-CoV, SARS-CoV-2 may enter the central nervous system via the systemic circulation or via the cribriform plate of the ethmoid bone.[53] Some COVID-19 patients have signs and symptoms of intracranial infection, such as dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia and seizure.[57,58] Apart from the central nervous system, increasing evidence demonstrates that coronavirus can invade peripheral nerve endings and cause damage, and subsequently gain access to other tissues.[59] Taste impairment, smell impairment, vision impairment and nerve pain were the main peripheral nervous system manifestations.[57]

By the end of April 2021, the international literature contained reports of 73 patients with COVID-19 presenting with concurrent Guillain Barré syndrome (GBS) .[60] Most had early stage COVID-19 with mild respiratory symptoms. One case report described a COVID-19 patient without any respiratory symptoms, but with loss of smell and taste preceding GBS.[61] Apart from direct cell injury, viral infection can lead to increase in the activity of sensory nerves as well as change in gene expression causing alterations in sensory nerve phenotype.[62] There is increasing evidence to show that viral

infections, especially of the respiratory tract, are likely to be associated with neuroplasticity within both the sensory and autonomic systems.[63] It is therefore likely that SARS-CoV-2 may impair the function of peripheral nerve endings around the taste buds via a direct effect and/or neuroplasticity, thus causing taste disturbance in COVID-19 patients. However, it is important to state that the impairment of the taste cells and the peripheral nerve injury is temporary, as most of COVID-19 patients fully recover from taste disturbance. Nerve regeneration is robust even after the nerve is injured[64] and taste buds can regenerate from stem cells either outside the taste buds or from remnants of the taste buds. However, given the lack of convincing demonstration of ACE2 receptor expression on the taste cell membrane or innervating nerves, the virus probably does not cause taste loss through direct infection of these cells. Instead, taste buds might be damaged by inflammation caused by the infection.

Inflammatory responses and taste

SARS-CoV-2 infected cells induce inflammation locally and systemically [65] and activation of inflammatory pathways can alter taste bud homeostasis. For example, systemic inflammation could reduce the number of stem cells which leads to reduction of numbers and function of taste buds in animal studies.[46,66] If SARS-CoV-2 directly infects tongue cells, the local inflammatory process could alter stem cell properties and ultimately influence taste perception. Data have suggested that taste disturbance might be a result of insufficient taste receptor cell renewal due to SARS-CoV-2 infection.[67] Inflammatory cytokines are important regulators of taste organs, and taste cells are acutely sensitive to inflammatory factors.[68] During viral infections, elevated levels of inflammatory cytokines may induce profound changes in the physiology and related behaviours of the taste organs.[69] Several inflammatory cytokine receptors such as tumour necrosis factor (TNF), interferon (IFN), interleukins (IL) 1, 6, 10 and 12 and toll-like receptors (TLR) are widely expressed in different types of taste cell.[70,71] Cytokines such as IL-10 and IL-1 play critical roles in maintaining the structural integrity of the peripheral gustatory system and normal taste function after nearby injury.[72,73] In contrast, TNF-α, IFN-γ and IL-6 have been shown in an animal model to be capable of inhibiting taste cell renewal, decreasing proliferation of progenitor taste cells and shortening the lifespan of taste cells.[71] TNF receptors 1 and 2, expressed in taste cells, are modulated by the TNF signalling pathway that is involved in amiloride-sensitive and insensitive sodium salt transport systems in the cells.[69] This pathway may contribute to taste disturbance associated with infections and inflammatory disease, as an elevation of TNF-α could decrease the sodium salt flux in the polarised taste cells with subsequent changes in sodium salt taste function.[66] IFNs are a group of signalling proteins that are produced and released by host cells in response to the presence of viral infection. IFNs play an important role in antiviral immunity, including SARS-CoV-2 infection, and IFN therapy is considered as a potential treatment against COVID-19. However, virally induced IFNs, acting either locally or systemically, could directly act on the receptors of taste cells via TLR and IFN pathways therefore (1) affect their cellular function in taste transduction, (2) induce premature death of taste cells or (3) skew the representation of different taste cell types, and subsequently lead to the development of taste disturbance.[70,74]

ACE2 and taste dysfunction

After the SARS-CoV-2 has gained access to host cells via interaction with ACE2 receptors, the virus then downregulates ACE2 expression on the cell surface so that this enzyme is unable to exert protective effects in the tissues.[75] As a result, some of the acute tissue injures in COVID-19 patients are thought to be due to the locally increased level of uncoupled angiotensin II activity.[76,77] The exact mechanism remains unknown. Both animal and human studies of influenza, respiratory syncytial virus and SARS-CoV reveal that downregulation of ACE2 expression may promote acute lung injury.[78–80] A study of 12 COVID-19 patients suggested that downregulation of ACE2 may be associated with high viral load and severe lung injury.[77] The local effects of downregulation of ACE 2 could facilitate this damaging effect or delay cell turnover. Reducing uncoupled angiotensin II proteins by the administration of ACE2 seems to

alleviate tissue damage in some situations.[80] Such a process might occur in the taste buds, as the RAAS plays an important role in the taste process as mentioned above. Furthermore, ACE2 and aminopeptidase N are RAAS proteases that facilitate proteolytic cleavage of proteins and peptides that are involved in the taste perception.[81] These proteases activate the taste receptors by releasing the residues from proteolysis of tastants. After SARS-CoV-2 infection, ACE2 is shown to be internalised into cytoplasm upon virus binding, thereby reducing the ACE2 availability in the cell membrane.[82] Taste disturbance may be as a result of insufficient RAAS proteases activity due to internalization of the ACE2 receptors by SARS-CoV-2 infection. Moreover, imbalance of the circulating ACE2 caused by the internalisation of the ACE2 receptors promotes the activation of aldosterone. The salivary glands respond to the aldosterone by reabsorbing sodium. The reabsorption of sodium results in the osmotic reabsorption of water, which might alter the salivary flow and then lead to hyposalivation and taste disturbance. This hypothesis suggests that overactivation of the RAAS lead to both xerostomia and taste disturbance due to high levels of ACE2 and aldosterone.[83,84] Therefore, taste disturbance might occur as a result of taste cell injuries, ACE2 downregulation, insufficient RAAS proteases activity and overactivation of the RAAS. However, SARS-CoV-2-infected patients exhibit loss of all taste perception, suggesting that the effect of ACE2 on particular taste cells may not be a major contributor. The pathogenesis of COVID-19 in patients taking RAAS-inhibitors is controversial and the effects of these inhibitors on ACE2 remain uncertain. Current evidence does not support concerns that the use of RAAS inhibitors is associated with an increased risk of SARS-CoV-2 infection or poor prognosis.[85] COVID-19 patients with cardiovascular diseases are advised to continue their RAAS inhibitors, since the inappropriate discontinuation of, or changes in medication, might lead to changes in blood pressure or the progression of related diseases.[86]

Conclusion

Taste buds may be potential targets of SARS-CoV-2 since most studies have shown many important proteins of the RAAS are highly expressed in taste buds. The underlying pathogenetic mechanisms of taste disturbance in COVID-19 patients may be due to direct but temporary taste cell and peripheral nerve ending damage, inflammatory responses and dysregulation of ACE2. However, more studies are needed before conclusive evidence is provided.

Authors' contributions

GG developed the concept of this paper and wrote the draft manuscript with LM. AP and AR reviewed and edited the draft. All authors gave their final approval and agree to be accountable for all aspects of the work.

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Author information:
Guangzhao Guan: Department of Oral Diagnostic and Surgical Sciences, Faculty of Dentistry, University of Otago, Dunedin, New Zealand.
Alison Mary Rich: Department of Oral Diagnostic and Surgical Sciences, Faculty of Dentistry, University of Otago, Dunedin, New Zealand.
Ajith Polonowita: Department of Oral Diagnostic and Surgical Sciences, Faculty of Dentistry, University of Otago, Dunedin, New Zealand.
Li Mei: Department of Oral Sciences, Faculty of Dentistry, University of Otago, Dunedin, New Zealand.
Corresponding author:
Guangzhao Guan, BDS, MBChB, DClinDent (Oral Medicine); Department of Oral Diagnostic and Surgical Sciences, Faculty of Dentistry, University of Otago, 310 Great King Street, Dunedin, 9016, New Zealand
simon.guan@otago.ac.nz
URL:
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REFERENCES

1. Tang A, Tong ZD, Wang HL, et al. Detection of Novel Coronavirus by RT-PCR in Stool Specimen from Asymptomatic Child, China. Emerg Infect Dis. 2020;26(6).
2. Chen W, Lan Y, Yuan X, et al. Detectable 2019-nCoV viral RNA in blood is a strong indicator for the further clinical severity. Emerg Microbes Infect. 2020;9(1):469-473.
3. Santarpia JL, Rivera DN, Herrera VL, et al. Aerosol and surface contamination of SARS-CoV-2 observed in quarantine and isolation care. Sci Rep. 2020;10(1):12732.
4. Transmission of SARS-CoV-2: A Review of Viral, Host, and Environmental Factors. Ann Intern Med. 2021;174(1):69-79.
5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
6. Shang J, Wan Y, Luo C, et al. Cell entry mechanisms of SARS-CoV-2. Proc Natl Acad Sci U S A. 2020.
7. Zou X, Chen K, Zou J, et al. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020:1-8.
8. Sato T, Ueha R, Goto T, et al. Expression of ACE2 and TMPRSS2 Proteins in the Upper and Lower Aerodigestive Tracts of Rats: Implications on COVID 19 Infections. The Laryngoscope. 131: E932-E939.
9. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020;12(1):8.
10. Gautier J-F, Ravussin Y. A New Symptom of COVID-19: Loss of Taste and Smell. Obesity. 2020;28(5):848-848.
11. Xydakis MS, Dehgani-Mobaraki P, Holbrook EH, et al. Smell and taste dysfunction in patients with COVID-19. Lancet Infect Dis. 2020:S1473-3099(1420)30293-30290.
12. Giacomelli A, Pezzati L, Conti F, et al. 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.
13. Lechien JR, Chiesa-Estomba CM, De Siati DR, 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. 2020:1-11.
14. Yan CH, Faraji F, Prajapati DP, et al. Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. Int Forum Allergy Rhinol. 2020. 10(7):806-813.

15. Shigemura N. Modulation of Taste Responsiveness by Angiotensin II. Food Sci Technol. 2015;21:757-764.
16. Shigemura N. Taste Sensing Systems Influencing Metabolic Consequences. Curr Oral Health Rep. 2017;4(2):79-86.
17. Vandenbeuch A, Clapp TR, Kinnamon SC. Amiloride-sensitive channels in type I fungiform taste cells in mouse. BMC Neurosci. 2008;9(1):1.
18. Roper SD, Chaudhari N. Taste buds: cells, signals and synapses. Nat Rev Neurosci. 2017;18(8):485-497.
19. Sainz E, Korley JN, Battey JF, et al. Identification of a novel member of the T1R family of putative taste receptors. J Neurochem. 2001;77(3):896-903.
20. Matsunami H, Amrein H. Taste and pheromone perception in mammals and flies. Genome Biol. 2003;4(7):220.
21. Go Y, Satta Y, Takenaka O, et al. Lineage-specific loss of function of bitter taste receptor genes in humans and nonhuman primates. Genetics. 2005;170(1):313-326.
22. Teng B, Wilson CE, Tu YH, et al. Cellular and Neural Responses to Sour Stimuli Require the Proton Channel Otop1. Curr Biol. 2019;29(21):3647-3656.e3645.
23. Ishimaru Y. Molecular mechanisms of taste transduction in vertebrates. Odontology. 2009;97(1):1-7.
24. Nomura K, Nakanishi M, Ishidate F, et al. All-Electrical Ca(2+)-Independent Signal Transduction Mediates Attractive Sodium Taste in Taste Buds. Neuron. 2020;106(5):816-829.e816.
25. Peng Y, Gillis-Smith S, Jin H, et al. Sweet and bitter taste in the brain of awake behaving animals. Nature. 2015;527(7579):512-515.
26. Spielman A, Brand J. Wiring taste receptor cells to the central gustatory system. Oral Dis. 2018;24(8):1388-1389.
27. Lee H, Macpherson LJ, Parada CA, et al. Rewiring the taste system. Nature. 2017;548(7667):330-333.
28. Shigemura N. Angiotensin II and taste sensitivity. Jpn Dent Sci Rev. 2015;51(2):51-58.
29. Zou X, Chen K, Zou J, et al. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020;14(2):185-192.
30. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181(2):271-280.e278.
31. Shigemura N, Takai S, Hirose F, et al. Expression of Renin-Angiotensin System Components in the Taste Organ of Mice. Nutrients. 2019;11(9).
32. Mariz B, Brandão TB, Ribeiro ACP, et al. New Insights for the Pathogenesis of COVID-19-Related Dysgeusia. J Dent Res. 2020;99(10):1206.
33. Wang Z, Zhou J, Marshall B, et al. SARS-CoV-2 Receptor ACE2 Is Enriched in a Subpopulation of Mouse Tongue Epithelial Cells in Nongustatory Papillae but Not in Taste Buds or Embryonic Oral Epithelium. ACS Pharmacol Transl Sci. 2020;3(4):749-758.
34. Chandrashekar J, Kuhn C, Oka Y, et al. The cells and peripheral representation of sodium taste in mice. Nature. 2010;464(7286):297-301.
35. Ossebaard CA, Smith DV. Amiloride suppresses the sourness of NaCl and LiCl. Physiol Behav. 1996;60(5):1317-1322.
36. Herness MS. Aldosterone increases the amiloride-sensitivity of the rat gustatory neural response to NaCl. Comp Biochem Physiol Comp Physiol. 1992;103(2):269-273.
37. Lin W, Finger TE, Rossier BC, et al. Epithelial Na+ channel subunits in rat taste cells: localization and regulation by aldosterone. J Comp Neurol. 1999;405(3):406-420.
38. Kaschina E, Unger T. Angiotensin AT1/AT2 receptors: regulation, signalling and function. Blood Press. 2003;12(2):70-88.
39. de Gasparo M, Catt KJ, Inagami T, et al. International union of pharmacology. XXIII. The angiotensin II receptors. Pharmacol Rev. 2000;52(3):415-472.
40. Shigemura N, Iwata S, Yasumatsu K, et al. Angiotensin II modulates salty and sweet taste sensitivities. J Neurosci. 2013;33(15):6267-6277.
41. Klopfenstein T, Kadiane-Oussou NJ, Toko L, et al. Features of anosmia in COVID-19. Med Mal Infect. 2020;50(5):436-439.
42. Vaira LA, Deiana G, Fois AG, et al. Objective evaluation of anosmia and ageusia in COVID-19 patients: Single-center experience on 72 cases. Head & Neck. 2020;42(6):1252-1258.
43. Hintschich CA, Wenzel JJ, Hummel T, et al. Psychophysical tests

reveal impaired olfaction but preserved gustation in COVID-19 patients. Int Forum Allergy Rhinol. 2020;10(9):1105-1107.

44. Butowt R, von Bartheld CS. Anosmia in COVID-19: Underlying Mechanisms and Assessment of an Olfactory Route to Brain Infection. Neuroscientist. 2020:10738584 20956905-1073858420956905.
45. Hamamichi R, Asano-Miyoshi M, Emori Y. Taste bud contains both short-lived and long-lived cell populations. Neuroscience. 2006;141(4):2129-2138.
46. Feng P, Huang L, Wang H. Taste bud homeostasis in health, disease, and aging. Chem Senses. 2014;39(1):3-16.
47. Perea-Martinez I, Nagai T, Chaudhari N. Functional cell types in taste buds have distinct longevities. PLoS One. 2013;8(1):e53399-e53399.
48. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The Lancet. 2020;395(10224):565-574.
49. Castillo-Azofeifa D, Losacco JT, Salcedo E, et al. Sonic hedgehog from both nerves and epithelium is a key trophic factor for taste bud maintenance. Development. 2017;144(17):3054-3065.
50. Fan D, Chettouh Z, Consalez GG, et al. Taste bud formation depends on taste nerves. eLife. 2019;8:e49226.
51. Desforges M, Le Coupanec A, Dubeau P, et al. Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System? Viruses. 2019;12(1).
52. Li K, Wohlford-Lenane C, Perlman S, et al. Middle East Respiratory Syndrome Coronavirus Causes Multiple Organ Damage and Lethal Disease in Mice Transgenic for Human Dipeptidyl Peptidase 4. J Infect Dis. 2016;213(5):712-722.
53. Netland J, Meyerholz DK, Moore S, et al. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol. 2008;82(15):7264-7275.
54. Lau KK, Yu WC, Chu CM, et al. Possible central nervous system infection by SARS coronavirus. Emerg Infect Dis. 2004;10(2):342-344.
55. Verstrepen K, Baisier L, De Cauwer H. Neurological manifestations of COVID-19, SARS and MERS. Acta Neurol Belg. 2020;120(5):1051-1060.
56. Kim JE, Heo JH, Kim HO, et al. Neurological Complications during Treatment of Middle East Respiratory Syndrome. J Clin Neurol. 2017;13(3):227-233.
57. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):683-690.
58. Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020;87:18-22.
59. Li YC, Bai WZ, Hirano N, et al. Coronavirus infection of rat dorsal root ganglia: ultrastructural characterization of viral replication, transfer, and the early response of satellite cells. Virus Res. 2012;163(2):628-635.
60. Abu-Rumeileh S, Abdelhak A, Foschi M, et al. Guillain-Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. J Neurol. 2021;268(4):1133-1170.
61. Scheidl E, Canseco DD, Hadji-Naumov A, et al. Guillain-Barré syndrome during SARS-CoV-2 pandemic: A case report and review of recent literature. J Peripher Nerv Syst. 2020;25(2):204-207.
62. Zaccone EJ, Undem BJ. Airway Vagal Neuroplasticity Associated with Respiratory Viral Infections. Lung. 2016;194(1):25-29.
63. Lee LY, Yu J. Sensory nerves in lung and airways. Compr Physiol. 2014;4(1):287-324.
64. Benga A, Zor F, Korkmaz A, et al. The neurochemistry of peripheral nerve regeneration. Indian J Plast Surg. 2017;50(1):5-15.
65. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol. 2020; 20(6):355-362
66. Kumarhia D, He L, McCluskey LP. Inflammatory stimuli acutely modulate peripheral taste function. J Neurophysiol. 2016;115(6):2964-2975.
67. Cooper KW, Brann DH, Farruggia MC, et al. COVID-19 and the Chemical Senses: Supporting Players Take Center Stage. Neuron. 2020;107(2):219-233.
68. Kaufman A, Choo E, Koh A, et al. Inflammation arising from obesity reduces taste bud abundance and inhibits renewal. PLoS

Biol. 2018;16(3):e2001959.

69. Feng P, Jyotaki M, Kim A, et al. Regulation of bitter taste responses by tumor necrosis factor. Brain Behav Immun. 2015;49:32-42.
70. Wang H, Zhou M, Brand J, et al. Inflammation and taste disorders: mechanisms in taste buds. Ann N Y Acad Sci. 2009;1170:596-603.
71. Cohn ZJ, Kim A, Huang L, et al. Lipopolysaccharide-induced inflammation attenuates taste progenitor cell proliferation and shortens the life span of taste bud cells. BMC Neurosci. 2010;11:72.
72. Shi L, He L, Sarvepalli P, et al. Functional role for interleukin-1 in the injured peripheral taste system. J Neurosci Res. 2012;90(4):816-830.
73. Feng P, Chai J, Zhou M, et al. Interleukin-10 is produced by a specific subset of taste receptor cells and critical for maintaining structural integrity of mouse taste buds. J Neurosci. 2014;34(7):2689-2701.
74. Wang H, Zhou M, Brand J, et al. Inflammation activates the interferon signaling pathways in taste bud cells. J Neurosci. 2007;27(40):10703-10713.
75. Vaduganathan M, Vardeny O, Michel T, et al. Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19. N Engl J Med. 2020;382(17):1653-1659.
76. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res. 2020; 81(5):537-540
77. Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020;63(3):364-374.
78. Glowacka I, Bertram S, Herzog P, et al. Differential Downregulation of ACE2 by the Spike Proteins of Severe Acute Respiratory Syndrome Coronavirus and Human Coronavirus NL63. Virol J. 2010;84(2):1198-1205.
79. Yang P, Gu H, Zhao Z, et al. Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury. Sci Rep. 2014;4:7027.
80. Gu H, Xie Z, Li T, et al. Angiotensin-converting enzyme 2 inhibits lung injury induced by respiratory syncytial virus. Sci Rep. 2016;6:19840.
81. Luchiari HR, Giordano RJ, Sidman RL, et al. Does the RAAS play a role in loss of taste and smell during COVID-19 infections? Pharmacogenomics J. 2021;21(2):109-115.
82. Bian J, Li Z. Angiotensin-converting enzyme 2 (ACE2): SARS-CoV-2 receptor and RAS modulator. Acta Pharmaceutica Sinica B. 2021;11(1):1-12.
83. da Silva Pedrosa M, Sipert CR, Nogueira FN. Altered taste in patients with COVID-19: The potential role of salivary glands. Oral Dis. 2021;27 Suppl 3:798-800.
84. Sunavala-Dossabhoy G. Renin-angiotensin II-aldosterone axis in SARS-CoV-2-associated xerostomia. Oral Dis. 2020; 10.1111.
85. Zhang J, Wang M, Ding W, et al. The interaction of RAAS inhibitors with COVID-19: Current progress, perspective and future. Life Sci. 2020;257:118142.
86. Wang JJ, Edin ML, Zeldin DC, et al. Good or bad: Application of RAAS inhibitors in COVID-19 patients with cardiovascular comorbidities. Pharmacol Ther. 2020;215:107628.