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Review Article

Taste Dysfunction in SARS-CoV-2 Infected Patients: A Review of Possible Pathological Mechanisms and Implications

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ABSTRACT

The coronavirus disease 2019 (COVID-19) is a pandemic infectious disease threatening the world, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While fever, cough, fatigue and shortness of breath are common symptoms, a sudden chemosensory (taste and/or smell) dysfunctions are increasingly reported in asymptomatic individuals that later test positive for COVID-19. The exact pathogenesis of these chemosensory disorders in SARS-CoV-2 infected patients has not yet been clarified. This review aims to provide a brief review of recent evidence for pathological mechanisms of the taste dysfunction in COVID-19 patients. We also discuss the possibility of using isolated sudden onset of taste alterations as an early symptom of SARS-CoV-2 infection that might be very helpful for reducing the spread of COVID-19 through early identification.

Keywords: Taste alteration, Gustatory Dysfunction, SARS-CoV-2, COVID-19, Pathological Mechanisms.

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INTRODUCTION

Concerning the outbreak of 2019 novel coronavirus (2019-nCoV), started in December 2019 in Wuhan, China, with a cluster of unknown pneumonia patients [1]. World Health Organization (WHO) officially announced the virus and disease names, "SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus 2)" and "COVID-19 (Corona Virus Disease 2019)" [2]. On March 11th 2020, WHO declared COVID-19 officially a pandemic. Now, this pandemic has rapidly spread all over the world.

On April 23rd 2020, the Centers for Disease Control and Prevention (CDC) has updated "new loss of taste or smell" to the list of symptoms for SARS-CoV-2 infection, "These symptoms of COVID-19 may appear 2-14 days after exposure to the virus: fever, cough, shortness of breath or difficulty breathing, chills, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell" [3].

Despite the widespread and highly contagious nature of SARS-CoV-2 infection, the current diagnostic tests: real time reverse transcription

polymerase chain reaction (RT-PCR), and chest computed tomography (CT) scan, used to identify the infected patients lack sensitivity [4]. The elevated rates of discordant test results and possible for false negatives or insufficient RT-PCR testing capability sometimes make it difficult for healthcare workers to identify individuals correctly for treatment [5].

Given the uncertainty in SARS-CoV-2 diagnostic testing, particular attention to additional clinical signs of SARS-CoV-2 infection may be helpful [5]. Several studies suggested that sudden gustatory or olfactory dysfunctions could represent early symptoms of COVID-19, occurring as the first presenting signs or commonly within 2-4 days after the clinical onset [6-11]. Moreover, SARS-CoV-2 infected patients may have loss of smell or taste as the only symptom [12]. Therefore, taste and smell dysfunctions may well serve as early diagnostic signs to identify asymptomatic patients that could possibly pass undetected through the healthcare system without triggering COVID-19 protocols [5].

To serve as an early warning symptom of infection, it is definitely important to understand the pathophysiology of SARS-CoV-2 induced taste and smell dysfunctions [5].

Taste and smell dysfunctions, collectively known as chemosensory disorders, are alterations of the normal gustatory and olfactory functioning [13]. Taste (or gustation) is the perception of salty, bitter, sour, sweet, and umami stimuli. Gustatory dysfunctions are divided into quantitative and qualitative taste disturbances [14].

Chemosensory disturbances are a common occurrence, taste alterations can be associated with several medical conditions (e.g., upper respiratory viral infection, malignancies, diabetes mellitus, Parkinson disease, Alzheimer disease, heart disease, asthma, liver and kidney diseases, candidiasis, chronic hepatitis C virus infection, hypothyroidism, or depression) [15, 16]. In addition, various medications are known to interfere with gustatory function [17].

Recent evidence suggests that chemosensory disorders induced by SARS-CoV-2 infection may be affected through mechanisms different from those employed by other coronaviruses, rhinoviruses, or influenza [18-20]. Compared to acute cold patients, gustatory functions are obviously worse in SARS-CoV-2 infected patients, in fact, not only global but also sweet and in specific bitter gustatory scores have been shown to differentiate well between COVID-19 and acute cold patients [21].

Taste dysfunction in COVID-19 patients

A multicenter European study reported a high prevalence of gustatory dysfunction during the SARS-CoV-2 pandemic (88.8% of affected patients) [8]. However, a great variability has been found in the incidence of taste dysfunction that probably depends on the country, methodology, and study [22]. These taste disturbances have included complete loss of taste (ageusia) or partial loss of taste (hypogeusia), and altered taste perception (dysgeusia) [8, 23].

Moreover, several studies reported that gustatory dysfunction was significantly more common among females, younger and non-hospitalized individuals with mild or moderate severity [8-10, 24]. Recovery of gustatory function commonly occurs within 3 weeks in most patients [9]. However, severe hypogeusia or ageusia can persist for more than 60 days [25].

Molecular virology of SARS-CoV-2

SARS-CoV-2 is a pleomorphic, enveloped, positive-sense, single-stranded ribonucleotide acid (RNA) virus [26]. It belongs to the coronavirus family (Coronaviridae) from a possible bat origin, with a genetic sequence very similar to severe acute respiratory syndrome corona virus (SARS-CoV) [26].

SARS-CoV-2 is thought to enter the host cell by a surface receptor known as angiotensin converting enzyme 2 (ACE2) [27], which is binds to the spike glycoprotein (S protein) on the viral envelope, the virus then enters the host cell through endocytosis [28].

However, it requires a second protein known as transmembrane protease serine 2 (TMPRSS2) that primes and cleaves the S protein, allowing fusion of the viral envelope with the endosomal compartment of the host cell [28].

ACE2 receptor has been detected in the cell membrane of several human organs and tissues including the lungs, upper respiratory tract, liver, kidneys, epithelial cells of the tongue and salivary glands, skeletal muscle, and nervous system [29-31].

A recent analysis of human genomes suggests potential associations between genetic polymorphisms in ACE2 and TMPRSS2 proteins with COVID-19 susceptibility, severity, and prognosis [32]. Studies of bitter, sour, sweet and umami taste bud cells have been shown to express ACE2 receptors but little to no TMPRSS2 proteins, however, show a strong expression of cathepsins L and B that might operate as proteases to cleave S protein of SARS-CoV-2 virus [18].

Pathological mechanisms of taste dysfunction in SARS-CoV-2 infected patients

The exact mechanisms of pathogenesis for taste dysfunction in COVID-19 patients are not yet known [5]. We would like to share some hypotheses regarding possible pathological mechanisms, which can be further investigated.

The potential role of salivary glands

SARS-CoV-2 has been detected in saliva and salivary glands [33]. ACE2 receptors have been found in the epithelium of taste bud cells and salivary glands [29]. Salivary glands have been demonstrated to be an early target for SARS-CoV [34], and SARS-CoV RNA has been shown to be present in saliva before lung lesions [35]. Moreover, salivary glands have also been demonstrated to serve as potential reservoirs for COVID-19 asymptomatic infection that may originate from infected saliva [30].

Therefore, salivary glands may be affected early by SARS-CoV-2 infection leading to salivary glands dysfunction with salivary flow rate and composition disturbances (quality and quantity), and the resultant taste alterations as an early symptom in COVID-19 asymptomatic patients [23, 36].

Involvement of the peripheral nervous system (PNS)

Affection of the PNS has been documented in SARS-CoV-2 infected patients [37]. The SARS-CoV-2 cytopathic effect could affect the peripheral neuronal path of the taste tract in 2 ways: (1) direct damage of the taste bud cells where ACE2 receptors are highly expressed, SARS-CoV-2 might also hamper the synthesis of neurotransmitters (dopamine and serotonin) by ACE2 expressing cells [38], or (2) direct damage of the cranial nerves responsible for taste perception (CN VII, IX, or X). Among these, damage to chorda tympani (CN VII) might be the most probable explanation [23]. Based on this hypothesis, SARS-CoV-2 virus initially colonizes the nasopharynx, then moves through the eustachian tube and eventually colonize the middle ear, causing damage to the chorda tympani and the subsequent dysgeusia [23].

Involvement of the central nervous system (CNS)

Despite SARS-CoV-2 RNA has been detected in the cerebrospinal fluid of COVID-19 patients [37], involvement of the CNS seems less likely due to the manifestations of such involvement (e.g., encephalitis/meningitis) in SARS-CoV-2 infected patients are rare and usually last longer than taste impairment [38].

Role of olfactory dysfunctions

The reported taste disorders in SARS-CoV-2 infected patients have only been subjective in nature, and it remains unknown if affected patients have actual disorders in their taste sensation [36], or whether they are experiencing alteration in flavor, which is a

"complex combination of the olfactory, gustatory, and trigeminal sensations perceived during tasting" as defined by the International Standards Organization [39].

Indeed, much of what is perceived as a taste disorder is actually a primary disorder in olfaction [40], resulting in defect of flavor sensation that consist of a combination of the food's taste, smell, texture, and temperature [41].

Many studies indicated that gustatory dysfunction was reported concurrently with olfactory dysfunction during the SARS-CoV-2 pandemic [8, 12, 42]. However, the prevalence of taste dysfunction would be higher than smell dysfunction in almost all studies [8, 42, 43]. This finding could lead to the suggestion that the association between the 2 dysfunctions is not so close, and that there are other factors in these patients behind the taste disturbances [44].

For these reasons, it has been hypothesized that the pathogenesis of taste dysfunction in COVID-19 patients is largely smell-independent [45]. The ability of SARS-CoV-2 to induce gustatory disorders in the absence of olfactory disturbances is a unique peculiarity for a virus. Therefore, sudden isolated gustatory disorders are highly specific of SARS-CoV-2 infection [45].

Role of pro-inflammatory cytokines

The average life span of taste bud cells is 10 days and renew continuously from a population of stem cells in the oral epithelium [46, 47]. Inflammatory mediators especially pro-inflammatory cytokines such as interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), and interleukin 6 (IL-6) can impede stem cell proliferation and decrease the lifespan of mature taste bud cells [48].

Since elevated levels of IFN-γ, TNF-α, and IL-6 have been seen in serum of laboratory-confirmed cases of SARS-CoV-2 infected patients [49], it has been suggested that these pro-inflammatory cytokines may lead to taste alterations [5]. Since the severity of SARS-CoV-2 infection is proportional to serum levels of these pro-inflammatory cytokines, the quality and severity of taste dysfunction may help in identifying mild, moderate, and severe cases that can be confirmed using molecular diagnostic testing [5].

Involvement of ACE2 receptor and taste renin-angiotensin system (RAS)

ACE2 has been identified as the cellular receptor for SARS-CoV-2 [27]. The role of ACE2 in modulating taste perception has been highlighted in many studies analyzing the chemosensory side effects of ACE2 inhibitors [50], and angiotensin II receptor blockers (ARBs) [51].

Remarkably, ACE2 receptor was expressed in the oral cavity, more apparently in epithelial cells of the tongue, when compared to other oral sites such as buccal and gingival mucosa. ACE2 receptor was also strongly expressed in taste bud cells [29, 52].

RAS system components are expressed in taste bud cells, and directly implicated in taste conduction [53]. Significantly, ACE2 mediates the conversion of angiotensin II [angiotensin (1-8)], a pro-inflammatory vasoconstrictor, to angiotensin (1-7), an anti-inflammatory vasodilator [54-56]. The interaction of SARS-CoV-2 with ACE2 receptor downregulates ACE2 expression, leading to a corresponding increase in inflammatory angiotensin II via unopposed ACE2, and a decrease in anti-inflammatory angiotensin (1-7) due to downregulated ACE2 (***Figure 1***) [57]. ACE2 also converts angiotensin I [angiotensin (1-10)] into angiotensin (1-9), which is then converted to angiotensin (1-7) by ACE1 [56].

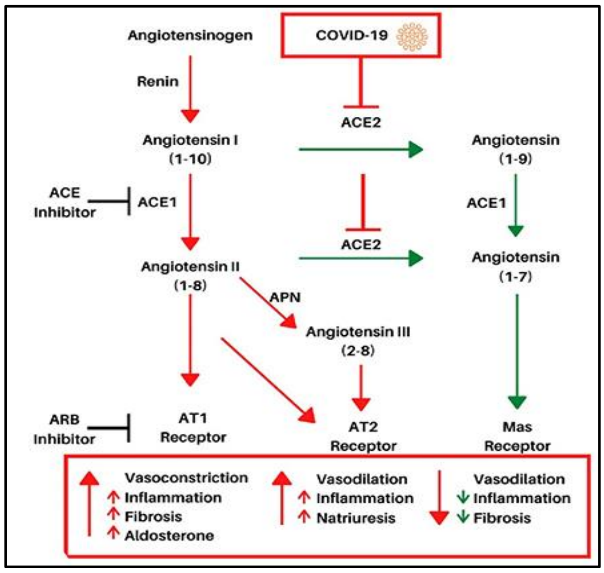

Figure 1. A schematic representation of the Renin-Angiotensin System (RAS) and its interaction with SARS-CoV-2 [5].

This imbalance between angiotensin II and angiotensin (1–7) has been hypothesized to play an important part in the unfavorable progression of patients with SARS-CoV-2 infection as it may increase inflammation and vasodilation in tissues expressing ACE2 receptor such as the lungs, and this imbalance in inflammation may also include the tongue, oral cavity, and nasal passages as these tissues are known to express ACE2 receptor as well [5].

This provides a plausible explanation for the taste dysfunction in COVID-19 patients as SARS-CoV-2 might enter taste bud cells via ACE2 receptor: as a consequence, increasing inflammation, cell death, or distorting the activity of the RAS system, which is a key player in taste sensitivity modulation [5, 58, 59].

Involvement of sialic acid receptors

SARS-CoV-2 could bind with the sialic acid receptors through its S protein [60]. Sialic acid is an essential component of the normal salivary mucin, and protects the glycoproteins that carry gustatory particles inside the taste buds from premature enzymatic degradation [61]. Moreover, reduced amount of sialic acid in the saliva is associated with an increase in the gustatory threshold, and impairs the ability to taste [62].

For these reasons, it has been hypothesized that SARS-CoV-2 may produce dysgeusia via interaction with sialic acid receptors on the taste buds. Following this occupancy, the gustatory particles degrade at a higher rate with subsequent increase in the gustatory threshold [44].

Side effect of certain drugs

It has been suggested that taste disturbances in COVID-19 patients may be due to drugs prescribed for this viral illness rather than from the actual infection [63]. Many SARS-CoV-2 infected patients take drugs including antibiotics or antipyretics, some of them is well-known to impair smelling/tasting [17]. However, taste dysfunction occurs also in drug-free patients, so this suggestion remains unsupported [38].

Role of local zinc deficiency

An interesting hypothesis underlying taste disorders in COVID-19 patients is related to zinc, which is thought to play a critical role in taste perception [23]. Zinc deficiency is well-known to cause taste dysfunction, because one of the enzymes essential to maintain taste sensation is a zinc dependent metalloenzyme called carbonic anhydrase [64]. During infection, zinc chelation through immune mechanisms and inflammatory processes may result in acute hypozincemia [65], or a more localized change in cellular zinc homeostasis of oral gustatory cells [65]. This may cause taste disorders similar to what has been noticed in association with other processes leading to zinc deficiency [66]. In patients with taste alterations, some randomized controlled trials have shown benefit of zinc supplementation [67].

For these reasons, it has been hypothesized that immune responses to SARS-CoV-2 viral replication can lead to changes in localized cellular zinc homeostasis in oral gustatory cells, which might also

be accompanied by hypozincemia, leading to taste dysfunction [23].

Moreover, zinc has been shown to inhibit coronavirus RNA polymerase activity in vitro [68], and is believed to play a role in antiviral immunity [69]. Therefore, zinc supplementation could play a significant role in prophylaxis and treatment of COVID-19 [70].

CONCLUSION

Taste alterations are considered as frequent, highly specific early symptoms of SARS-CoV-2 infection that might be helpful for reducing the spread of COVID-19 through early identification. Several mechanisms have been hypothesized for the SARS-CoV-2 induced taste dysfunction. Since the exact pathogenesis of chemosensory dysfunctions in COVID-19 patients has not yet been clarified, further long-term follow-up studies on patients with these disorders are needed in order to understand the underlying pathological mechanisms that will help in taking preventive measures and developing effective treatment modalities.

Disclaimer

The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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