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Review Article

Pathogenesis of Gustatory and Olfactory Dysfunction in Coronavirus Disease 2019 Patients: A Neurophysiological Hypothesis

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ABSTRACT

Coronavirus disease 2019 (COVID-19), the global pandemic, has taken a toll on health and socioeconomic status of the entire world. Clinical spectrum and outcome of this disease still remain a mystery. Centers for Disease Control and Prevention has recently included olfactory and gustatory dysfunction in the key symptoms suggestive of COVID-19 infection. In spite of various studies since the outbreak of this disease, the exact pathological mechanism of this ailment is yet unclear. Cyclic adenosine monophosphate (cAMP), the ubiquitous protein essential for many biological processes, has been proved as a key factor in signal transduction of taste and smell as well as in viral replication. This article hypothesizes that virus utilizes cAMP for its replication in oral and olfactory mucosa resulting in depleted level of cAMP available for transmission of chemosensory impulse and thereby resulting in dysregulated taste and smell in COVID-19 patients.

Key words: ACE2 receptor, Coronavirus disease 2019, Cyclic adenosine monophosphate, Gustatory dysfunction, Insular cortex, Olfactory dysfunction

INTRODUCTION

Coronavirus disease 2019 (COVID-19), a zoonotic infection caused by SARS-CoV-2, started as an outbreak in Wuhan, China, in December 2019 and quickly became an epidemic. Within no time, it attained pandemic status to shudder the entire world and has caused an unprecedented and unimaginable psychosocial impact on millions of people. Clinical spectrum of COVID-19 is exceedingly varied and can range from asymptomatic form to severe multiorgan dysfunction and failure. In extremes of life and in people who are immunologically compromised, the disease can run a fatal course. In symptomatic cases, the disease manifests as fever, dry cough, tiredness, and shortness of breath which appears 2–14 days after exposure. Mild-to-moderate symptomatic cases, if not treated adequately, may progress to more severe condition within a couple of days leading to dire consequences. Unfortunately, there are no specific clinical symptoms to secernate COVID-19 from other viral respiratory infections.

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Chemosensory dysfunction was not a commonly reported symptom from the initial epicenter of COVID-19. Subsequently, both olfactory and gustatory dysfunctions were found to be prevailing in patients with mild-to-moderate infection. The American Academy of Otolaryngology-Head and Neck Surgery and The British Association of Otorhinolaryngology are now recommending these symptoms to be added to the list of primary screening symptoms for COVID-19.[1,2] Centers for disease control and prevention has recently included olfactory and gustatory dysfunction in the key symptoms for COVID-19 infection.

Olfactory and gustatory dysfunction may appear before, during, or after the general symptoms. The altered taste

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sensation in COVID-19 varies from decreased sensitivity to taste (hypogeusia), taste confusion (dysgeusia), or complete loss of taste (ageusia). Altered smell sensation can be in the form of reduced ability to detect odors (hyposmia), complete inability to detect odors (anosmia), change in the normal perception of odors (parosmia), or sensation of an odor that is not present (phantosmia). Gustatory and olfactory dysfunction can occur as a separate entity or in combination in COVID-19 patients with a patent nasal airway with or without other clinical presentations.[3]

The altered chemosensory perception in COVID-19 patients is sudden in onset and majority of cases shows fast recovery, but few cases of delayed recovery have also been reported. Olfactory and gustatory dysfunction unassociated with rhinorrhea and nasal obstruction suggests a distinguishable mechanism from that of other viral infections. The pathophysiological mechanisms leading to the olfactory and gustatory dysfunctions in COVID-19 infections are still obscure. This paper tries to elucidate the probable mechanism for altered olfactory and gustatory dysfunction in COVID-19 patients.

HYPOTHESIS FOR ALTERED TASTE AND SMELL PERCEPTION

In both the oral and olfactory epithelium, the SARS-CoV-2 virus utilizes the cyclic adenosine monophosphate (cAMP) for replication. This utilization of cAMP hampers with the generation of action potential in response to taste and smell. The level of utilization of cAMP depends on viral load and the immune status of the patient, and depending on these parameters, there can be different grades of altered sensation. The alteration will be transient as action potential is prevented from reaching the brain and not due to direct injury to the receptor cells [Figure 1]. Virus reaches the brain through the olfactory nerves, eventually affecting the thalamus and the brain stem.

SARS-CoV-2 virus can enter the nerve cell either by direct fusion or penetration of plasma membrane or by endocytosis. Virus initially attacks the peripheral nerve terminals and then gradually ascends through the afferent nerves of gustatory and olfactory sense to reach the brain. This explains the lack of recovery of both taste and smell sensation even after weeks or months.

EVALUATION OF HYPOTHESIS

cAMP is a universal second messenger found in many life forms including microorganisms, plants, animals, and humans. This biological regulator controls multiple cytokinetic processes such as cell differentiation and

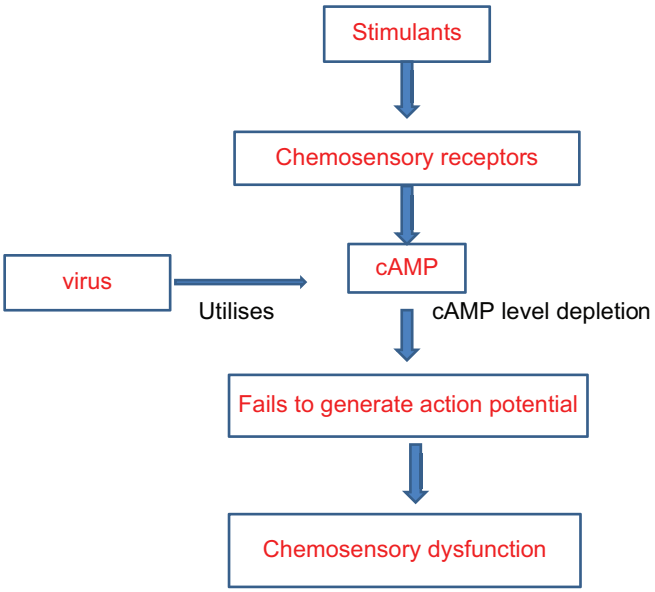

Figure 1: Schematic representation of Viral-induced chemosensory dysfunction

proliferation, ionic influx, excitability, gene expression, and cell-specific processes such as glycogenolysis and lipolysis.[4,5] The role of recently identified exchange protein directly activated by cAMP (EPAC) in viral infection was first reported in Middle East respiratory syndrome coronavirus (MERS-CoV). EPAC protein has been reported to regulate the replication of MERS-CoV.[6] Blocking of exchange proteins directly activated by cAMP in MERS-CoV has shown to stop viral replication.[5]

ACE 2, the specific binding site for SARS-CoV-2, is abundantly expressed in olfactory epithelium and epithelial lining of tongue.[7,8] Spike protein of the virus binds with ACE 2 receptors to set off chemical changes, which results in the fusion of host and viral cell membranes and facilitates viral entry into host cells.[9] The previous studies have shown viral infiltration into the brain through olfactory nerves, affecting the thalamus and brain stem. Once higher centers of CNS are affected it results in prolonged loss of taste and smell.[10]

Physiology of Gustatory Sensation

Gustatory sensation is perceived by taste buds which are a group of modified epithelial cells called taste cells. At resting stage, taste cell membrane is negatively charged inside and positively charged outside. Taste cells are stimulated by binding of chemicals to their receptor proteins to cause depolarization of taste cell which generates action potential to be transmitted to central nervous system. Taste impulse from anterior two-third of tongue passes through lingual nerve, chordae tympani, and facial nerve to reach nuclei of tractus solitarius. Impulse from posterior one-third of tongue and posterior region of mouth and throat is

transmitted through glossopharyngeal nerve to the tractus solitarius. Taste from base of tongue and pharyngeal region is conveyed through the vagus nerve. All these fibers synapse at tractus solitarius, and from there reaches the ventral posterior medial (VPM) nucleus of thalamus and then to postcentral gyrus of parietal cerebral cortex and finally into Sylvian fissure and opercular insular area in cerebral somatic area of frontal lobe.[11]

When gustatory stimulants bind with their respective receptors, adenylyl cyclase will be activated and induce the release of intracellular second messenger cAMP. This activates protein kinase A which further leads to activation of cation channels. This results in cellular depolarization and generation of action potential which leads to an increase Ca^{2+} or Na^{+} influx through voltage-gated membrane channels resulting in release of cations from intracellular stores. In response to this cation release, neurotransmitters are secreted, which generates action potentials in afferent nerve fibers to the brain [Figure 2].[12,13]

Physiology of Olfactory Sensation

Olfactory cells (bipolar nerve cells) derived from central nervous system are receptors of smell sensation. The odorant substance which comes in contact with the olfactory membrane binds with receptor protein and activates adenylyl cyclase which converts ATP into cAMP. cAMP activates sodium ion channel and thereby increases electrical potential inside the cell membrane and excites olfactory nerve and this impulse relays into central nervous system. Olfactory nerves penetrate the small foramina in the cribriform plate of the ethmoid bone to enter the cranial cavity. In the cranial cavity, the olfactory nerve fibers enter the olfactory bulb, where it synapses with the mitral cells, to form collections known as synaptic glomeruli. Axons of mitral cells leave the olfactory bulb to form olfactory tract which runs backward to end in olfactory cortex, located on the base of frontal lobe and medial aspect of temporal lobe. From the olfactory cortex, olfactory sensation is relayed via the mediodorsal nucleus of the thalamus to the insular and orbitofrontal cortex. The insular cortex also receives taste input from the medial part of VPM nucleus and is considered to be the site of integration of olfactory and taste information to produce the sensation called flavor.[11,14]

Binding of olfactory stimulants to its receptors releases cAMP, which activates cationic channels leading of cation influx and results in membrane depolarization. This excites the olfactory nerve which is transduced to the CNS. Action potential frequency in both gustatory and olfactory nerves is proportional to the concentration of specific sensory molecules. Action potential frequency will be attenuated by adaptation or desensitization of the receptor and reduced production of cAMP leads to taste and smell dysfunction [Figure 2].[15]

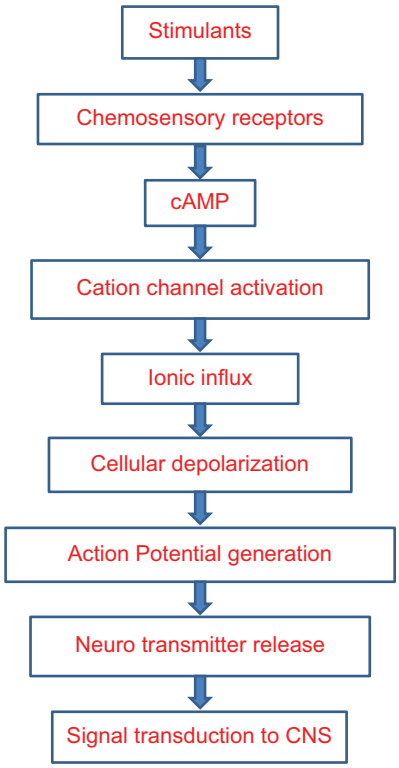

Figure 2: Schematic representation of normal chemosensory perception

CONCLUSION

The clinical spectrum as well as the long-term clinical consequences and the molecular mechanism of this ailment are still to be discerned. Studies have shown exhortatory results in preventing the viral replication by blocking exchange proteins directly activated by cAMP in MERS-CoV. The same stratagems may be applied against SARS-CoV-2 and cAMP can be utilized as a therapeutic target in COVID-19 patients which could reduce viral replication and thereby improving taste and smell dysfunctions. Elaborate follow-up studies of COVID-19 patients should be undertaken to comprehend more about chemosensory dysfunction, as these could be initial or the only reported symptoms.

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