AIJR Preprints
Section: Coronavirus
Article Id: 78, Version: 1, 2020
URL:https://preprints.aijr.org/index.php/ap/preprint/view/78

{Click on above link to see the latest available version of this article}

NOT PEER-REVIEWED

The Bitter the Taste, The Better is the Medicine: Is Caffeine the Answer to COVID-19?

Devyani Sharma[1], Ashutosh Bansal [2]

[1]Department of Anatomy, All India Institute of Medical Sciences, New Delhi 110029, India.

[2] Department of Cardiac Biochemistry, All India Institute of Medical Sciences, New Delhi 110029, India.

First Author's Full Name: Devyani Sharma
Highest Qualification: Master's Degree
Post/Rank (If a student, provide the course name and course year): Ph.D., First year
Affiliation (College/University/Institute) with postal address: Department of Anatomy, All India Institute of Medical Sciences, New Delhi 110029, India.
Email id: **********

Second Author's Full Name: Ashutosh Bansal
Highest Qualification: Master's Degree
Post/Rank (If a student, provide the course name and course year):Junior Research Fellow
Affiliation (College/University/Institute) with postal address: Department of Cardiac Biochemistry, All India Institute of Medical Sciences, New Delhi 110029, India.
Email id:******

Version 1: Received: 16 May 2020 / Approved: 17 May 2020 / Online: 18 May 2020

ABSTRACT

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus. The virus is mainly transmitted through droplets generated when an infected person coughs, sneezes, or exhales. The firsthand reason for COVID 19 is upper respiratory dysfunction which allows the entry of viruses in the respiratory system and leads to severe problems in the human body. Thus, Bitter taste receptor, TAS2Rs on human airway smooth muscle (ASM) found in the respiratory system can play a big role in providing immunity against COVID-19. Activation of TAS2Rs by bitter agonists activates host defense pathways through calcium signaling. Cytokines storms is the another reason for COVID -19 that can be prevented by TAS2Rs because it can regulate natural killer cell-mediated cytotoxicity, chemokine signaling pathways, T cell receptor signaling pathways, TNF signaling pathways, and others. Since, we propose to utilize caffeine, the bitter agonists to stimulate the TAS2Rs, activating host defense mechanisms and also suppressing the cytokine storms due to its anti-inflammatory action, altogether leading to an ameliorated effects of COVID-19.

Keywords: COVID-19, Taste Receptor (TAS2Rs), caffeine

1. Introduction

The current outbreak of COVID-19 caused by 2019-coronavirus has led to tremendous loss to mankind and hence declared pandemic. Human coronaviruses (hCoVs) can be divided into low pathogenic and highly pathogenic corona viruses. The low pathogenic CoVs infect the upper respiratory tract whereas highly pathogenic hCoVs shows severe pneumonia-like symptoms which are often associated with rapid virus replication, massive inflammatory cell infiltration and elevated pro-inflammatory cytokine/chemokine responses further resulting in Acute Lung Injury (ALI), and Acute Respiratory Distress Syndrome (ARDS) [1]. The morbidity, mortality, and transmissibility of this novel coronavirus remain unharmonious [2][3]. Due to the unavailability of effective anti-viral therapies; affordable, safe, and effective medicines are urgently required for COVID- 19.

2. Active role of TAS2Rs in airway cells

Very recently, it was concluded that 2019-nCoV replicates efficiently in the upper respiratory tract. Airway Smooth Muscle Cells (ASMCs), a structural component of the walls of all the airways within the bronchial tree which controls the diameter of the pulmonary airways by contraction/relaxation. Hypercontraction of ASMCs leads to airway constriction and obstruction. In humans, ASMC's G-protein coupled receptor (GPCR) family named type 2 taste receptors (TAS2Rs), are critical role players in host defense pathways [4][5]. Previously, TAS2Rs, whose ligands are bitter substances, were thought to be expressed only on the tongue. However, recent studies demonstrated that they are highly expressed in extra-oral tissues as well [4]. This indicates that TAS2Rs might have functions other than bitter taste perception in the biological system. The most dominant subtypes of TAS2Rs in humans are TAS2R10; 14 and 31 and their activation by bitter tastants induces significant broncho-dilatory effects. Together, bitter agonists are considered as a novel class of bronchodilators in the treatment of obstructive airway diseases [5].

Apart from this, it has been found that TAS2R10 is involved not only in controlling several infectious diseases caused by bacteria, viruses, and parasites, but also in various types of cancers which suggests that TAS2R10 may be a key trigger of host defense pathways. Many researchers have arrived at a similar consensus [6]. Altogether, these findings suggest that TAS2Rs may robustly regulate human innate immunity and trigger host defenses to control the infection [4]. Therefore, TAS2R10 can be a useful target model to identify the function of bitter taste receptor agonists. And thus, we propose to utilize bitter agonists to fight COVID-19.

3. Efficacy of caffeine

Caffeine, a widely accepted bitter-tasting compound having methyl-xanthine alkaloid is tremendously attracting the attention due to its variety of physiological and pharmacological activities. It can be one of the effective agonists to trigger the host defense pathway by targeting TAS2Rs. To date, the upper respiratory tract is the most important door to be closed for fighting against preventing this deadly disease. Therefore, we believe that activating bitter receptors can be an effective approach to prevent the deadly virus from efficiently replicating in the upper respiratory tract. Other studies have shown that TAS2Rs can also activate the robust calcium-dependent secretion of Anti- Microbial Peptides (AMPs), including β-defensin-1 and 2, in the epithelial cells of the respiratory tract. AMPs can vigorously block the interaction between a virus and its receptor. Therefore, interpretation of the complete signaling pathways linking TAS2R receptors on ASM cells and further their activation through IP3 receptors and Ca^{2+}sensitivity may be beneficial in the identification of novel protectant bronchodilators functioning through the TAS2R receptors [7]. Caffeine is long known to be beneficial in preventing and treating apnea and bronchopulmonary dysplasia in newborns.

Also, a cytokine storm is another key event causing the death of patients infected with coronavirus [1]. Thus, inhibiting overactive immune responses can also be very important in these fatalities from preventing cytokine storms. Thankfully, Caffeine also acts as an anti-inflammatory agent by non-selectively inhibiting the phosphodiesterases (PDEs). Briefly, the Inhibition of PDEs raises the intracellular concentration of cyclic AMP (cAMP), which downstream activates protein kinase A and inhibits leukotriene synthesis. This leads to reduced inflammation and enhanced innate immunity. It also raises cyclic guanosine monophosphate levels in the body, thus relaxing smooth muscle, dilating airways, and lowering pulmonary arterial pressure[8]. Taken together, Available data suggest that caffeine remains the mainstay in the prevention of respiratory health problems.

Apart from this, A report suggests the antiviral activities of caffeine by inhibiting viral protein synthesis [9] and suppressing plaque formation by interfering with the cell-to-cell transmission in certain viruses such as poliovirus, influenza virus, HSV-1, vaccinia virus, Newcastle Disease Virus (NDV), Japanese encephalitis virus and adenovirus. Similar to TNF or octyl gallate, Caffeine preferentially accelerates the cytopathic effects (CPE) and the death of virus-infected cells by selective apoptosis.

Surprisingly, Caffeine can also interfere with virus multiplication after viral DNA replication, probably at the formation of progeny infectious virus step, because similar results were observed when the multiplication of HSV-1 was inhibited by ammonium chloride or Brefeldin A during the formation of infectious progeny virus after viral DNA replication and nucleocapsid formation [10].

4. Conclusion

So, are we skipping a conclusive link? Can the reason be our thought process which is stopping us to believe that the prevention of this pandemic cannot be that simple or is it that we have not explored this corner of the house. To conclude, we would like to attract the attention of our fellow researchers working globally to emphasize onto these possibilities and suggest the population, some more beneficial and easily accessible products that may minimize the deterioration, the Covid-19 could do, thereby, minimizing the loss to mankind. Just to add, the intake should be managed keeping all the other medical conditions of the subject in mind. Preferentially, a low but regular intake is what we would greatly recommend.

Conflict of interest

The authors declare no conflicts of interest regarding the publication of this paper.

How to Cite :

Devyani Sharma *et al.* The Bitter the Taste, The Better is the Medicine: Is Caffeine the Answer to COVID-19? *AIJR Preprints,*78, version 1, 2020.https://preprints.aijr.org/index.php/ap/preprint/view/78

References

[1] R. Channappanavar and S. Perlman, “Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology,” *Seminars in Immunopathology*, vol. 39, no. 5. Springer Verlag, pp. 529–539, Jul. 01, 2017, doi: 10.1007/s00281-017-0629-x.

[2] “The novel Chinese coronavirus (2019□nCoV) infections: Challenges for fighting the storm - Bassetti - 2020 - European Journal of Clinical Investigation - Wiley Online Library.” https://onlinelibrary.wiley.com/doi/full/10.1111/eci.13209 (accessed May 15, 2020).

[3] J. Parry Hamilton, “Wuhan: Britons to be evacuated as scientists estimate 44 000 cases of 2019-nCOV in the city,” doi: 10.1136/bmj.m351.

[4] P. Lu, C. H. Zhang, L. M. Lifshitz, and R. ZhuGe, “Extraoral bitter taste receptors in health and disease,” *Journal of General Physiology*, vol. 149, no. 2. Rockefeller University Press, pp. 181–197, 2017, doi: 10.1085/jgp.201611637.

[5] D. A. Deshpande *et al.*, “Bitter taste receptors on airway smooth muscle bronchodilate by localized calcium signaling and reverse obstruction,” *Nat. Med.*, vol. 16, no. 11, pp. 1299–1304, Nov. 2010, doi: 10.1038/nm.2237.

[6] X. Li, C. Zhang, L. Liu, and M. Gu, “Existing bitter medicines for fighting 2019-nCoV-associated infectious diseases,” *FASEB J.*, May 2020, doi: 10.1096/fj.202000502.

[7] X. Tan and M. J. Sanderson, “Bitter tasting compounds dilate airways by inhibiting airway smooth muscle calcium oscillations and calcium sensitivity,” *Br. J. Pharmacol.*, vol. 171, no. 3, pp. 646–662, Feb. 2014, doi: 10.1111/bph.12460.

[8] J. Evered, E. Pfeifer, and M. Gracianette, “Caffeine to prevent respiratory failure and improve outcome in infant pertussis Novel treatment (new drug/intervention; established drug/procedure in new situation),” *BMJ Case Rep*, 2018, doi: 10.1136/bcr-2017-223102.

[9] Z. Yamazaki and I. Tagaya, “Antiviral Effects of Atropine and Caffeine,” *J. Gen. Virol.*, vol. 50, no. 2, pp. 429–431, Oct. 1980, doi: 10.1099/0022-1317-50-2-429.

[10] A. Koyama *et al.*, “Effect of caffeine on the multiplication of DNA and RNA viruses,” *Mol. Med. Rep.*, vol. 1, no. 2, pp. 251–255, Mar. 2008, doi: 10.3892/mmr.1.2.251.