

Chloroquine and COVID-19: role as a bitter taste receptor agonist?

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Abstract

COVID-19 is a world public health emergency caused by the new coronavirus, SARS-CoV-2. Many drugs were repurposed as a treatment for COVID-19 patients including Chloroquine (CQ). CQ is a bitter taste receptor agonist reported to relax the airways suggesting a role in preventing disease severity of COVID-19 patients with asthma.

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Keywords: Airway relaxation, asthma, bitter taste receptor agonist, bronchodilation, Chloroquine, COVID-19, SARS-CoV-2, TAS2R

Original Submission: 11 January 2021; **Accepted:** 19 January 2021

Article published online: 24 January 2021

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To the Editor,

The world is facing a global health crisis with coronavirus disease 2019 (COVID-19) caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 infection was first identified in China in December 2019 [1] but quickly spread all over the world, affecting over 73 million persons and causing more than 1.6 million deaths [2]. Individuals with COVID-19 may experience different symptoms ranging from mild to severe illness including fever, cough, congestion, fatigue, loss of taste or smell, chest pain and difficulty breathing [3]. The disease severity depends on age, sex

and co-morbidities including chronic respiratory diseases [4]. Although the literature remains divided about the impact of asthma [5], chronic obstructive pulmonary disease is one of the most reported co-morbidities in individuals with COVID-19, and is related to disease severity, intensive care unit admission and mortality [6–8].

Chronic respiratory diseases are characterized by chronic airway inflammation and bronchial hyperresponsiveness that may lead to exacerbation following viral infections (VIs). VIs are known to affect dramatically both asthma and COPD [9,10], resulting in airway smooth muscle (ASM) contraction and airway obstruction. Indeed, VIs, including the common coronavirus, are responsible for up to 80% of asthma exacerbations [11]. Similarly, like other coronaviruses, SARS-CoV-2 may exacerbate asthma, although the underlying molecular mechanisms through which this may occur are still unknown [12]. SARS-CoV-2, infects bronchial epithelium causing tissue damage and mucus accumulation [13], so decreasing lung function [14]. In addition, asthma exacerbation has been reported to be associated with COVID-19 pneumonia [15,16] and mortality [17].

Even though vaccine campaigns started in the UK and USA for the most vulnerable individuals [18,19], a vaccine will not be available soon to all countries around the world. Specific treatments are lacking, but many drugs were repurposed to treat COVID-19, including antivirals (lopinavir, ritonavir, remdesivir), antibiotics (azithromycin, teicoplanin), chloroquine/hydroxychloroquine, glucocorticoids and bronchodilators [20]. In fact, the use of both reliever and controller treatments were increased in asthmatic children with COVID-19 compared with those without COVID-19 [21]. Moreover, physicians recommended and used bronchodilators to relax the airways of individuals with COVID-19 who have chronic respiratory diseases [22] to help them improve their health condition and reduce ventilator needs [16]. Chloroquine (CQ) is used for the treatment of different diseases, such as malaria, rheumatoid arthritis and systemic lupus [23] and it successfully inhibits the SARS-CoV-2 replication *in vitro* [24]. Although scientists remain divided on its efficacy against COVID-19, no harmful effect was demonstrated [25]. However, some studies concluded that CQ was effective in viral clearance and in improving COVID-19 patients' prognosis [26–28].

The beneficial effect of CQ is related to its role in immunomodulation and inhibition of viral replication [29]. On the other hand, CQ is a bitter taste receptor (TAS2R) agonist activating four receptor subtypes [30], expressed in extra-oral tissues including ASM and epithelium [31]. Moreover, their activation leads to relaxation of pre-contracted human ASM, similar to that induced by β_2

agonists [32], and prevention of airway hyper-responsiveness and mucus accumulation in a murine model of asthma [33]. Interestingly, the relaxation induced by TAS2R agonists is unaffected by β -agonist tachyphylaxis [34]. Of importance, many bitter compounds were suggested to be used to treat COVID-19 [35], and CQ efficacy was shown to decrease in obese individuals with COVID-19, where TAS2Rs are down-regulated [36]. No association between chronic respiratory diseases and severity of SARS-CoV-2 infection was observed when individuals with COVID-19 were treated with CQ [26,27,37].

These observations suggest that the TAS2R agonist, CQ, may have a role in airway relaxation, bronchodilation and in preventing disease severity of individuals with COVID-19.

Authors' contributions

BB conceptualized the study; BB and IR prepared the original draft and BB and RC reviewed and edited it. All authors read and approved the final version of the manuscript.

Acknowledgements

We would like to thank Dr Karen A. Pescatore (Rowan University, Glassboro, NJ, USA) for critically reading the manuscript.

Conflict of interests

The authors have no conflicts of interest to declare.

Funding

The authors received no specific funding for this work.

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