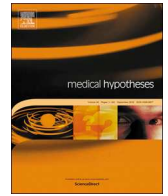




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## Letter to Editors

## Survival of COVID-19 patients requires precise immune regulation: The hypothetical immunoprotective role of nicotinic agonists



## ARTICLE INFO

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## ABSTRACT

Summary recent studies have provided novel evidence regarding the effect of nicotine agonists on the prevention or modulation of cytokines storm and reduction of infection. In this study we tried to attempt to address these issues from a therapeutic perspective of nicotine agonists in this manner and we describe one of the most challenging theories of immunotherapy in coronavirus-19 (COVID-19). The analysis of the proposed mechanism goes beyond the physiological consequences of a way to design new strategies to provide anti-inflammatory drugs.

## Introduction

Coronaviruses appear periodically and unpredictably from year 2002 with the onset of SARS-COV, and then with MERS-COV and now with COVID-19 (SARS-CoV-2). This family of viruses causing infectious diseases and they became a constant threat to human health. There is no definitive and approved treatment for cardiorespiratory sequels of these COV infections. Although from a pathophysiological point of view there is a deep understanding of the immune response to the virus, there is no approved treatment for immunomodulation in these patients thus it seems that treatment of immune system problems such as systemic pulmonary inflammatory responses associated with COV is necessitating. Immunity based treatment can be a good alternative and savior therapy to some antiviral treatment. As we know cytokine storms in lung tissue in most deadly events in patients with COV infection. Therefore, in cases of COV induced pneumonia, it is important to control cytokine production and inflammatory response. Although this strategy is challenging due to a lack of clear immune response and endangering the host defense, it does not seem impossible. In an attempt to address these issues from a therapeutic perspective, we describe our hypothesis about one of the most challenging theories of immunotherapy in COV viruses.

## Hypothesis

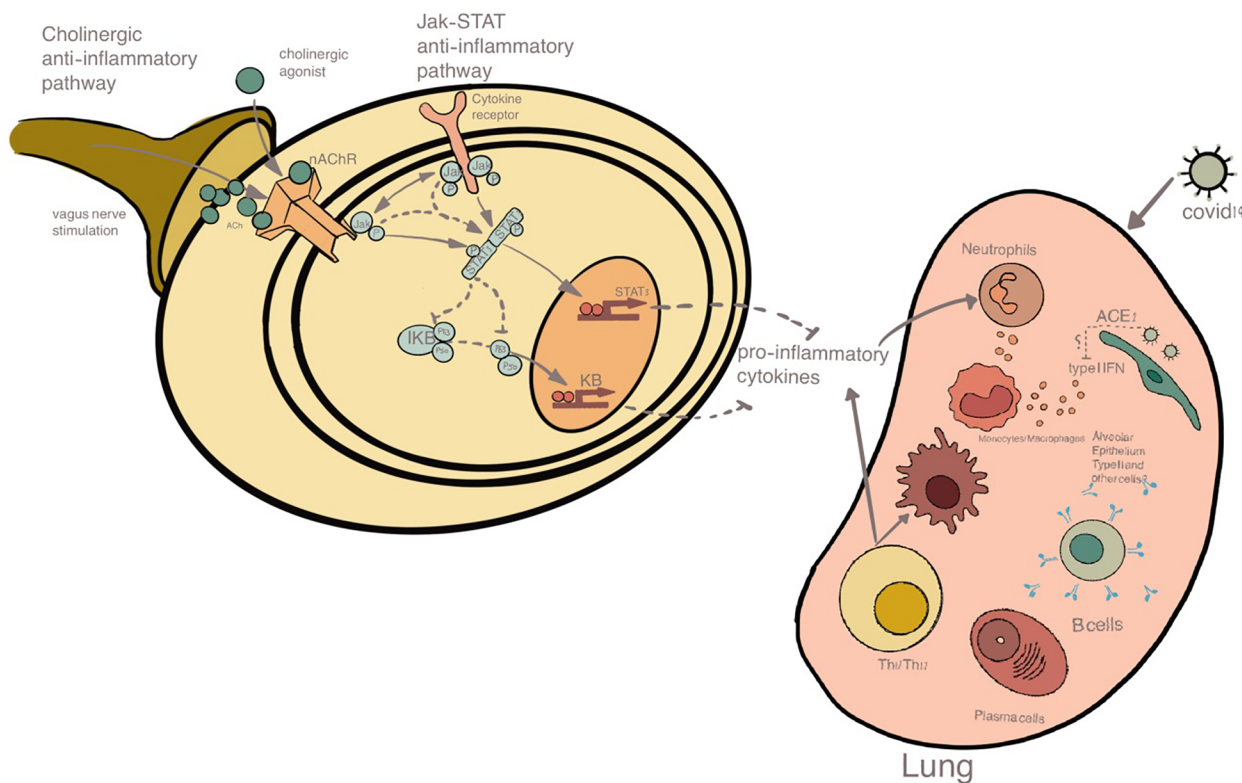
Replication of RNA viruses such as the COV family is accompanied by excessive production of interferons, neutrophils and macrophages

which brings about a massive immune response, referred to as “cytokine storm”. This overproduction negatively affects the balance of the inflammatory responses and the normal function of cytokines.

This immune system disorder can lead to series of symptoms including fever, edema, and hypotension in mild cases. In severe cases it can cause systemic inflammation, heart failure, pulmonary failure which consequently led acute respiratory syndrome and eventually death. In COVID-19 infection, like other coronavirus infections, a similar scenario is expected with varying degrees of immune interference.

It is expected that the management of the activity and performance of the cytokines might lead to the prevention of severe endothelial dysfunctions and pulmonary fibrosis in patients affected by COVID-19. Previous studies have demonstrated the indicated impressive relation between the nervous system and immune system. These studies demonstrated that nervous system has modulatory effects on the production of multiple inflammatory cytokines in lung tissue [1,2].

The cholinergic pathway, via acetylcholine neurotransmitters, can interact with nicotinic acetylcholine receptors. Further activation of these receptors can apply a suppressive effect on the production of pro-inflammatory cytokines [3] (Fig. 1). Among the nicotinic receptor subtypes, the subunit 7( $\alpha$ -7) is the most prominent due to its high expression in immune cells (B cells, macrophages, T cells, and target cells) and its association with humoral and intrinsic immunity. Therefore, evaluation of pharmacological approaches to activate  $\alpha$ -7nAChR for inhibition of immunologic phenomenon such as cytokine storm can be helpful. Nicotine is a non-selective agonist of this receptor that mimics



**Fig. 1.** The hypothetical cellular ‘COVID-19 inflammatory pathway’ virus with the influx of neutrophils and monocytes/macrophages results in the hyperproduction of pro-inflammatory cytokines. And “cytokine storm” occurs, weakened by the intensification of the immune system’s inflammatory response. But it seems that ‘nicotinic anti-inflammatory pathway’ triggered by the  $\alpha 7$  nAChR in immune cells during infection, bacterial components, or intracellular mediators trigger pro-inflammatory pathways that converge in the activation of the NF- $\kappa$ B, which will translocate into the nucleus and induce the transcriptional activation of a variety of inflammatory cytokines. Nicotine inhibits the production of pro-inflammatory cytokines in macrophages by mechanism dependent on the  $\alpha 7$ nAChR.

acetylcholine binding to stimulate vagal activity and decrease cytokine function and block the inflammatory pathway. The general algorithm of this idea was illustrated in Fig. 2. Hence, comprehension of this theory can provide better therapeutic guidance for the treatment of coronavirus infections, especially COVID-19.

**Discussion**

We describe one of the trends in the decline of the cytokine storm. It seems that lethality and uncontrolled complications of coronaviruses are due to the lack of control of the cytokine storms. Although the pathogenesis of coronaviruses is complex and requires specific treatment, previous studies have shown the efficacy of neutralizing anti-

inflammatory cytokines in inflammatory conditions caused by COVID-19 [1]. Dose-dependent anti-inflammatory effects of the 7nAChR-1 agonist have been demonstrated, and previous studies have shown that activation of this receptor can have an anti-inflammatory role and immune cells regulating [4]. Nicotine is agonist of mentioned receptor but cannot be used clinically due to its toxicity, addictive nature, and lack of specificity. Other agonists of 7nAChR-1 receptors in this group, such as GTS-21, produce the same nicotine effects without nicotine problems. Also some studies have reported limited use of GTS-21 in the clinical phase and have shown that this agent can cause a decrease of cytokine levels and significantly reduced inflammatory biomarker after infection [3,5]. It has been thought that a nicotine agonist compound like GTS-21 is able to suppress the production of pro-inflammatory

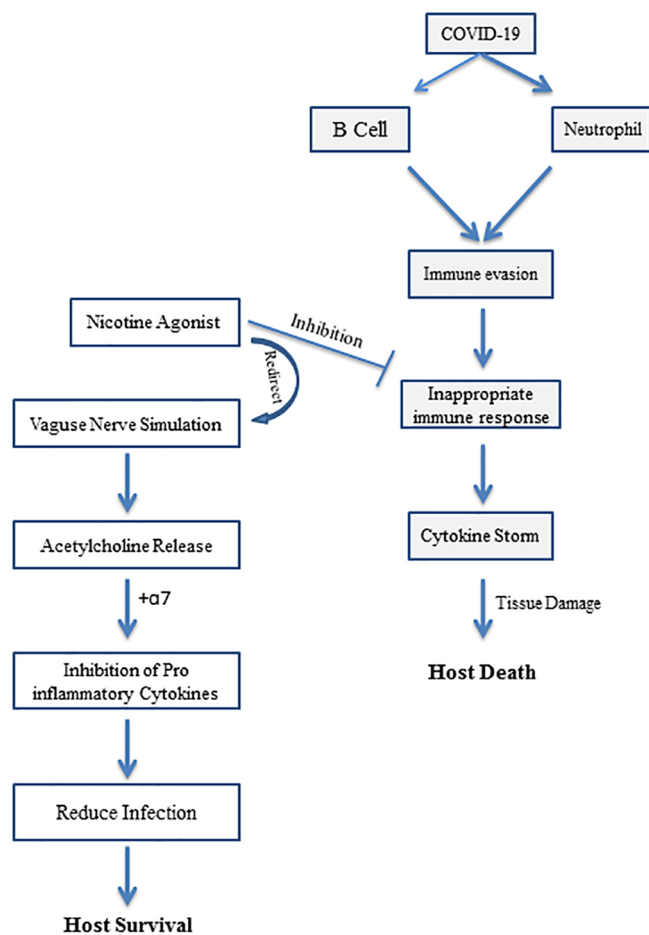


Fig. 2. Schematic design of the virus-induced inflammatory pathway which probably block by the nicotine agonist.

cytokines during infection of COVID-19. In fact, these nicotine agonists can control allergic inflammation induced by innate immune and cellular immune pathways. Taken together according to mentioned literature review it can be concluded that GTS-21, as potent 7nAChR-1

receptor agonist, will act as an anti-inflammatory agent against COVID-19- infection-induced cytokine storm and inflammatory disturbances in respiratory system and reduced the risk of death in infected subjects.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.109871>.

#### References

- [1] De Jonge W, Ulloa LJ. The alpha7 nicotinic acetylcholine receptor as a pharmacological target for inflammation. *Br J Pharmacol* 2007;151(7):915–29.
- [2] Ulloa L, Messmer DJC. High-mobility group box 1 (HMGB1) protein: friend and foe. *Cytokine Growth Factor Rev* 2006;17(3):189–201.
- [3] D'Elia RV, Harrison K, Oyston PC, Lukaszewski RA, Clark GC. Targeting the “cytokine storm” for therapeutic benefit. *Clin Vaccine Immunol* 2013;20(3):319–27.
- [4] Galle-Treger L, Suzuki Y, Patel N, Sankaranarayanan I, Aron JL, Maazi H, et al. Nicotinic acetylcholine receptor agonist attenuates ILC2-dependent airway hyperreactivity. *Nature Commun* 2016;7(1):1–13.
- [5] Kox M, Van Velzen JF, Pompe JC, Hoedemaekers CW, Van Der Hoeven JG, Pickkers PJ. GTS-21 inhibits pro-inflammatory cytokine release independent of the Toll-like receptor stimulated via a transcriptional mechanism involving JAK2 activation. *Biochem Pharmacol* 2009;78(7):863–72.

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