Inflammatory reflex disruption in COVID-19

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Abstract
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China, in late 2019 and caused coronavirus disease 2019 (COVID-19), which is still a global pandemic. In most infected people, SARS-CoV-2 only causes moderate symptoms, whereas in other patients, it leads to severe illness and eventually death. Although the main clinical manifestation of COVID-19 is often seen in the lungs, this disease affects almost all body organs. The excessive and prolonged release of inflammatory cytokines that might occur in COVID-19 patients, known as cytokine storms, stimulates undesired immune responses and can cause various tissues damage. In the current review article, we focus on the potential advantages of the intrinsic cholinergic anti-inflammatory pathway as the efferent arm of the inflammatory reflex in COVID-19 management. Considering this endogenous protective mechanism against chronic inflammation, we focused on the effects of SARS-CoV-2 in the destruction of this anti-inflammatory system. Several studies showed the interaction of SARS-CoV-2 with the alpha-7 subtype of the nicotinic acetylcholine receptor as the effector molecule of the inflammatory reflex. In contrast, neurological manifestations have increasingly been identified as significant extrapulmonary manifestations of COVID-19. The rational connection between these findings and COVID-19 pathogenesis might be an important issue in both our understanding of and dealing with this disease. COVID-19 is deeply rooted in our daily life and requires an urgent need for the establishment of effective therapeutic options, and all the possible treatments must be considered for the control of such inflammatory conditions.

KEYWORDS
autonomic dysfunction, cholinergic anti-inflammatory pathway, COVID-19, inflammatory reflex, SARS-CoV-2

INTRODUCTION

Coronavirus disease 2019 (COVID-19) and the virus that causes it (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) are two terms that have been heard every day for the past 2 years, and have affected all aspects of our lives. This virus is responsible for the recent global viral pneumonia outbreak and has caused an unprecedented disaster around the world. As of February 2022, COVID-19 has been confirmed in more than 420 million people worldwide.

Dysregulated overproduction of inflammatory cytokines, which is known as cytokine storm, especially in the lung tissue, is one of the main features and hallmarks of COVID-19. However, the association between factors and parameters that lead to cytokine storms remains to be elucidated. Cytokine storm is not an easily manageable condition, and contributes to mortality and morbidity in patients. During this pandemic outbreak, various treatments and drugs have been suggested to treat COVID-19 or reduce its symptoms. Targeting cytokine overproduction in COVID-19 has been the subject of recent
research, and some studies have had acceptable results, but most of the results are inconclusive due to the complexity of the processes.\textsuperscript{6–9} As a logical mechanism to control the release of the undesired cytokines, some studies investigated the role of the endogenous inflammatory reflex and the efferent arm of this reflex, which is called the “cholinergic anti-inflammatory pathway (CAP)” in the modulation of chronic inflammation\textsuperscript{10} (Figure 1). The alpha-7 subtype of the nicotinic acetylcholine receptor (α7nAChR), as the effector molecule of the CAP, has a special significance in this mechanism.\textsuperscript{11} Different cells or tissues expressing α7nAChR include the nervous system,\textsuperscript{12} immune cells, such as lymphocytes,\textsuperscript{13} monocytes\textsuperscript{14} and macrophages;\textsuperscript{15} and many different tissues, such as kidney,\textsuperscript{16} bladder,\textsuperscript{17} prostate,\textsuperscript{18} testicular,\textsuperscript{19} penile,\textsuperscript{20} cervical\textsuperscript{21} ovarian,\textsuperscript{22} uterine,\textsuperscript{23} gastric,\textsuperscript{24} colorectal,\textsuperscript{25} pancreas,\textsuperscript{26} liver\textsuperscript{27} and lung tissue.\textsuperscript{28} Regarding the activation of α7nAChR by nicotine, several studies have highlighted the low prevalence of smokers among COVID-19-infected patients.\textsuperscript{29} Thus, nicotine and other α7nAChR ligands might have therapeutic value in hospitalized COVID-19 patients; however, the efficacy of such nicotine-based treatments is inconsistent.\textsuperscript{30,31} In addition to such an interesting observation, to date, the CAP, as the efferent arm of the intrinsic inflammatory reflex, has been shown to inhibit the inflammatory response in many experimental and clinical experiments.\textsuperscript{32–34} This is why we suggest considering these relevant issues, and electrical or pharmacological activation of α7nAChR and potentiation of the CAP by inhibiting multiple inflammatory responses might protect against cytokine storm, and thus have therapeutic value in COVID-19 patients, and can be considered for the management of this global disaster. Here, we provide a review of potential interactions between the CAP and SARS CoV-2 infection in humans, with an update on potential interactions between these protective responses and outcomes in patients with COVID-19.

## INFLAMMATORY REFLEX CONCEPT

Approximately two decades ago, Borovikova et al. mechanically focused on the role of the central nervous system in the regulation of systemic inflammatory responses, and showed the existence of the CAP in an innovative animal study.\textsuperscript{35} In their experiment, the production of tumor necrosis factor-α as a pro-inflammatory cytokine was decreased in an endotoxin-treated animal model that received electrical stimulation of the vagus nerve.\textsuperscript{35} Further experiments showed that such reflexive anti-inflammatory effects are exerted through multiple neuroimmune interactions, which is called the inflammatory reflex.\textsuperscript{36} This reflex maintains immunological homeostasis through bidirectional communication between the brain and peripheral organs.\textsuperscript{37}

Recently, regulation of immune cell dynamics by the sympathetic nervous system has been reported.\textsuperscript{38} The molecular mechanism by which the vagus nerve negatively regulates inflammatory responses has been identified, and the cellular and molecular basis for the regulation of the immune system by the nervous system has been shown by Tracey et al.\textsuperscript{39} The mechanism was found to be mediated by the nicotinic acetylcholine receptor α7 subunit, which is expressed on macrophages in the spleen. In the inflammatory reflex, the action of the afferent vagus nerve residing in the nodose ganglion is activated by inflammatory cytokines. The signal is moved to the nucleus tractus solitarius. Mutual associations between the nucleus tractus solitarius and the dorsal motor nucleus of the vagus nerve cause the activation of efferent vagus nerve fibers from the dorsal motor nucleus.\textsuperscript{40} The signal is transmitted to the celiac ganglia and the superior mesenteric ganglion in the celiac plexus, where the nerve of the spleen originates. Norepinephrine released from this splenic nerve interacts with β2-adrenergic receptors, and causes the release of ACh from Ach-releasing T cells. ACh interacts with α7nAChRs on macrophages and inhibits proinflammatory cytokine and inflammation.\textsuperscript{40}

The detailed molecular mechanisms of inhibition of cytokine release by the inflammatory reflex have been investigated and highlighted in previous studies. Briefly, an extended range of inflammatory stimuli activates sensory neurons traveling to the brainstem through the afferent or sensory arm of the vagus nerve. After the transmission and arrival of these inputs to the brainstem, it generates action potentials that travel from the brain to the peripheral organs through the efferent or motor arm of the vagus nerve (Figure 1). At the end of the inflammatory reflex mechanism, the direct or indirect activation of α7nAChR through ACh suppresses the production of inflammatory mediators. The action potentials cause the release of ACh from vagus nerve terminals, as well as T cells containing functional choline acetyltransferase.\textsuperscript{40} Then, the produced ACh interacts with α7nAChR on immunocompetent cells to inhibit cytokine release (especially tumor necrosis factor, interleukin-1β, interleukin-6, and interleukin-18) from inflammatory cells.\textsuperscript{41} The α7nAChRs are expressed in macrophages and B- and T-lymphocytes, and as the effector molecule of the CAP, might represent a neuroimmune target in inflammatory diseases.\textsuperscript{13–15,42}

Early evidence in COVID-19 patients showed that the rate of infection in smokers is lower than the general population, suggesting potential protective effects of nicotine against SARS-CoV-2.\textsuperscript{43–45} Alexandris et al. proposed that repurposing the approved drugs for smoking cessation and neurological conditions might be a therapeutic strategy in severe COVID-19.\textsuperscript{46}

In addition to pharmacological activation of the inflammatory reflex, electrical vagus nerve stimulation is feasible, and appears as an interesting tool in the treatment of inflammatory diseases, and it seems that patients with a low vagal tone are more prone to complications of COVID-19.\textsuperscript{47} Many different studies have shown the benefit of pharmacological or electrical activation of the inflammatory reflex in the prevention of similar/related inflammatory conditions; for example, acute respiratory distress syndrome.\textsuperscript{48,49} Also, numerous studies have suggested that electrical or pharmacological potentiation of CAP through α7nAChR activation, using vagus nerve stimulation devices or exogenous α7nAChR agonists (such as nicotine or pharmacological compounds) could represent innovative therapeutic strategies to limit COVID-19-induced cytokine storm.\textsuperscript{50,51} Accumulated findings show that the inflammatory reflex drives a coordinated anti-inflammatory function, and show that its anti-inflammatory potential
might have therapeutic benefits against several bacterial and viral infections, and holds promise for treating COVID-19.

3 | SARS-COV-2 INTERACTION WITH \( \alpha 7nAChR \)

After the global outbreak of the COVID-19 pandemic, several experiments showed that the SARS-CoV-2 uses angiotensin-converting enzyme 2 receptor as the receptor to enter the cells.\(^{52,53}\) However, it might be of great importance to examine other potential interactions between the virus and other cell receptors. There is a great deal of evidence regarding the interactions between SARS-CoV-2 and nicotinic receptors.\(^{54}\) The so-called cholinergic anti-inflammatory reflex is a construct that is standing on the \( \alpha 7nAChR \). Some studies predict a direct interaction between SARS-CoV-2 spike glycoprotein with \( \alpha 7nAChR \), which could impair the effectiveness of CAP and initiate the cascade of events in COVID-19.\(^{55}\)

The data showing that the virus binds to the \( \alpha 7nAChR \) are interesting. Tanmay \textit{et al.} highlighted the idea that COVID-19 has similar characteristics to other inflammatory conditions that have imbalanced type 1 macrophages/type 2 macrophages ratios, and activation of \( \alpha 7nAChR \) in those diseases has shown alleviating impact.\(^{55}\) In COVID-19, immune dysregulation can be caused by the interaction of the underlying virus with the \( \alpha 7nAChR \) in type 1 macrophages that express \( \alpha 7nAChR \).\(^{56,57}\) Understanding the role of SARS-CoV-2 in impairing macrophage function through \( \alpha 7nAChR \) might provide better prospects for the design and dissemination of more effective therapy for COVID-19. Thus, the direct interaction of SARS-CoV-2 with \( \alpha 7nAChR \) and inhibition of its intracellular signaling pathways might...
participate in the pathogenesis of this disease. Most recently, the interaction between $\alpha_7nAChR$ and SARS-CoV-2 spike glycoprotein has been shown in innovative studies, and it was hypothesized that the dysregulation of CAP might be implicated in the pathophysiology of this disease.\textsuperscript{58} Farsalinos et al., by a set of computational molecular docking approaches, investigated the interaction between the SARS-CoV-2 spike glycoprotein and nAChR subunits.\textsuperscript{59} In that study, an interaction between the pentameric $\alpha_7nAChR$ and SARS-CoV-2 was observed.\textsuperscript{59} However, these studies are in silico modeling investigations, with no supportive evidence of interactions between $\alpha_7nAChR$ and SARS-CoV-2. Thus, the possibility that SARS-CoV-2 might interact with $\alpha_7nAChR$, supports the hypothesis of dysregulation of the CAP being implicated in COVID-19 pathogenesis. Identifying the detailed molecular interactions between SARS-CoV-2 and $\alpha_7nAChR$ could provide a rational basis for vaccine development, and accelerate the innovation of therapeutics against COVID-19.

4 | AUTONOMIC DYSFUNCTION IN COVID-19

The autonomic nervous system (ANS) consists of complex antagonistic components, and regulates many different physiological processes in response to internal or external stimuli. COVID-19 can cause several extrapulmonary manifestations, including central nervous system damage, and autonomic dysfunction is a prominent feature in moderate-to-severe COVID-19 disease.\textsuperscript{60,61} Table 1 summarizes different types, diagnostic methods and the range of complications of the nervous system in COVID-19 infection. The incidence range of nervous system complications varies in different studies and is calculated to be approximately 5–100% (Table 1). The immune system might influence ANS function and the local production of extremely high levels of inflammatory agents, including cytokines, chemokines and free radicals, that cause severe damage to the lungs and other organs of the human body, including ANS.\textsuperscript{62}

Both the sympathetic nervous system and parasympathetic nervous system might have been given a role in COVID-19, but here we are focusing on the parasympathetic nervous system.\textsuperscript{63,64} Autonomic dysfunction by impairing both afferent and efferent arms of the inflammatory reflex causes downstream effects that eventually benefit the virus or worsen the condition of the patient.\textsuperscript{65} In this regard, heart rate variability in the evaluation of autonomic balance might provide an important source of information in COVID-19.\textsuperscript{66–68} Mao et al. investigated the neurological manifestations of SARS-CoV-2 infection that were observed in almost 40% of the infected patients.\textsuperscript{69} Blood–brain barrier breakdown as a potential mechanism of SARS-CoV-2-induced neurological dysfunction was proposed in some studies.\textsuperscript{70,71} Thus, blood–brain barrier breakdown might lead to infiltrating the peripheral cytokines to access the central nervous system, where they might trigger or exacerbate neuroinflammation, as reported in some other experimental models, and could contribute to observed neurological manifestations and also increase susceptibility to autonomic dysfunction.\textsuperscript{72,73} In this regard, Liu et al. investigated the effects of stimulation of CAP in regulating autonomic functions and showed that vagus nerve stimulation through nAChR is capable to improves pulmonary function in an animal model of lung injury.\textsuperscript{74} Abrams and colleagues’ findings suggest that symptoms of small fiber neuropathy might develop during or shortly after COVID-19. Thus, autonomic dysfunction associated with COVID-19 infection might be derived from small fiber neuropathy and affects the function of CAP, and is associated with post-COVID-19 symptoms.\textsuperscript{75}

The neurological manifestations of COVID-19 and autonomic dysfunction after COVID-19 infection were highlighted in some early-stage experiments.\textsuperscript{76,77} More recently, the different aspects of autonomic dysfunction in SARS-CoV-2 infection and the timeline of the main findings in the issue were reviewed.\textsuperscript{78,79} It seems that, in up to 70% of survivors of COVID-19, the patients have one or more symptoms of post-viral autonomic dysfunction lasting for ≥3 months, which highlights the importance of monitoring ANS symptoms.\textsuperscript{60}

| Types of neurological manifestation | Diagnostic methods | Range of complications | Reference |
|-----------------------------------|--------------------|------------------------|-----------|
| Hypoxic encephalopathy            | Clinical symptom and laboratory findings | ～10% | 83 |
| Cerebral ischemic stroke          | MRI                | ～23%                   |           |
| Encephalopathy                    | Clinical symptom   | ～28%                   | 84 |
| Dysexecutive syndrome             | Clinical symptom   | ～36%                   |           |
| Brain perfusion abnormalities     | MRI                | ～100%                  |           |
| Cardiac or cerebrovascular disease| CT                 | ～10%                   | 85 |
| Acute cerebrovascular disease     | CT                 | ～5%                    | 86,87 |
| Encephalopathy                    | Clinical symptom   | ～5%                    | 88 |
| Acute cerebrovascular disease     | CT                 | ～10%                   | 69 |

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.
COVID-19 should be investigated in future experimental and clinical studies.

Last but not least, other reports are emerging suggesting the emergence of autoantibodies to G protein-coupled receptors in the autonomic nervous system. Dysregulation of these receptors of the autonomic nervous system might contribute to observed COVID-19 symptoms. Here, we highlighted the autonomic dysfunction as a non-respiratory symptom in COVID-19 infection and pointed out the protracted inflammatory response due to the associated immunosuppressive dysfunction. Altogether, ANS can be affected during SARS-CoV-2 infection, and autonomic dysfunction might be a possible complication in COVID-19 patients.

5 | CONCLUSIONS

As reviewed here, after highlighting the principles of the inflammatory reflex in maintaining immunological homeostasis, we focused on the inhibition of α7nAChR and autonomic dysfunction – both of which are caused by SARS-CoV-2 infection. This virus could interact with α7nAChR, causing dysregulation of the inflammatory reflex. Also, it can cause several extrapulmonary manifestations, including autonomic dysfunction (Figure 1). These manifestations might affect the endogenous protective mechanisms against deregulated pro-inflammatory cytokine secretion.

Knowledge of α7nAChR inhibition by the virus spike proteins, as well as autonomic manifestations of COVID-19, might be essential for early diagnosis and a better prognosis for COVID-19 patients, and might pave the way for the future establishment of novel therapeutic options. Altogether, there is enough evidence to conclude that α7nAChR inhibition by SARS-CoV-2 and neurological symptoms are two important features of SARS-CoV-2 infection. We suggest that activation of α7nAChR by vagus nerve stimulation (e.g. electrical or pharmacological) or perhaps α7nAChR agonists (e.g. nicotine, GTS-21, AR-R1779 etc.) might provide innovative interventions for the management of cytokine storm or pulmonary inflammation in COVID-19. At this point, the CAP is not convincingly linked with the pathogenesis or outcome of COVID-19 in well-designed clinical outcome studies or well-designed pathogenesis studies. However, as a rational concept, future efforts to develop COVID-19 therapies would be better suited if we redirect our attention to the inflammatory reflex concept and investigate the exact function in our body; more specifically, how it affects the α7nAChR functions or dysregulation of the ANS plays a key role in the pathophysiology of COVID-19.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

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