


REVIEW ARTICLE

Inflammatory reflex disruption in COVID-19

Khalil Hajiasgharzadeh^{1,2}  | Mahdi Jafarlou¹  | Behzad Mansoori³  |
Narges Dastmalchi⁴  | Behzad Baradaran^{1,5}  | Alireza Khabbazi² 

¹Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

²Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

³Cellular and Molecular Oncogenesis Program, The Wistar Institute, Philadelphia, Pennsylvania, USA

⁴Department of Biology, University College of Nabi Akram, Tabriz, Iran

⁵Pharmaceutical Analysis Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Correspondence

Behzad Baradaran, PhD, Immunology Research Center, Tabriz University of Medical Sciences, Golgasht St., Tabriz 5166614766, Iran.
Email: baradaranb@tbzmed.ac.ir

Alireza Khabbazi, PhD, Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Golgasht St., Tabriz 5166614756, Iran.
Email: dr_khabbazi@yahoo.com

Funding information

This study received no specific grant from any funding bodies.

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

1 | 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.¹ 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-19.² 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.³⁻⁵ 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.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 inflammation¹⁰ (Figure 1). The alpha-7 subtype of the nicotinic acetylcholine receptor ($\alpha 7nAChR$), as the effector molecule of the CAP, has a special significance in this mechanism.¹¹ Different cells or tissues expressing $\alpha 7nAChR$ include the nervous system;¹² immune cells, such as lymphocytes,¹³ monocytes¹⁴ and macrophages;¹⁵ and many different tissues, such as kidney,¹⁶ bladder,¹⁷ prostate,¹⁸ testicular,¹⁹ penile,²⁰ cervical,²¹ ovarian,²² uterine,²³ gastric,²⁴ colorectal,²⁵ pancreas,²⁶ liver²⁷ and lung tissue.²⁸ Regarding the activation of $\alpha 7nAChR$ by nicotine, several studies have highlighted the low prevalence of smokers among COVID-19-infected patients.²⁹ Thus, nicotine and other $\alpha 7nAChR$ ligands might have therapeutic value in hospitalized COVID-19 patients; however, the efficacy of such nicotine-based treatments is inconsistent.^{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.³²⁻³⁴ This is why we suggest considering these relevant issues, and electrical or pharmacological activation of $\alpha 7nAChR$ 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.

2 | INFLAMMATORY REFLEX CONCEPT

Approximately two decades ago, Borovikova *et al.* mechanistically 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.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.³⁵ Further experiments showed that such reflexive anti-inflammatory effects are exerted through multiple neuroimmune interactions, which is called the inflammatory reflex.³⁶ This reflex maintains immunological homeostasis through bidirectional communication between the brain and peripheral organs.³⁷

Recently, regulation of immune cell dynamics by the sympathetic nervous system has been reported.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.*³⁹ The mechanism was found to be mediated by the nicotinic acetylcholine receptor $\alpha 7$ subunit, which

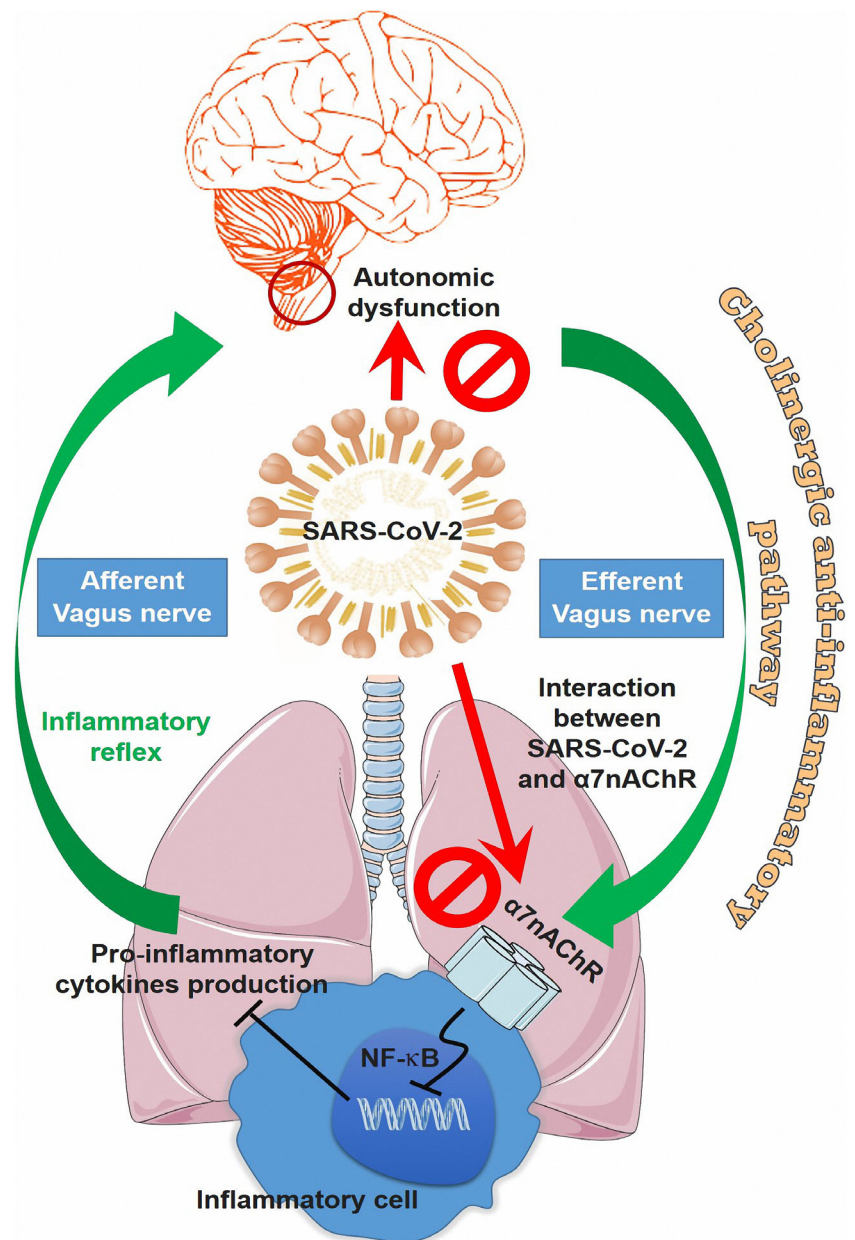
is expressed on macrophages in the spleen. In the inflammatory reflex, the action of the afferent vagus nerve residing in the nodose ganglion is activated by inflammatory cytokines. The signal is moved to the nucleus tractus solitarius. Mutual associations between the nucleus tractus solitarius and the dorsal motor nucleus of the vagus nerve cause the activation of efferent vagus nerve fibers from the dorsal motor nucleus.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 $\beta 2$ -adrenergic receptors, and causes the release of ACh from ACh-releasing T cells. ACh interacts with $\alpha 7nAChRs$ on macrophages and inhibits proinflammatory cytokine and inflammation.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 $\alpha 7nAChR$ 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.⁴⁰ Then, the produced ACh interacts with $\alpha 7nAChR$ on immunocompetent cells to inhibit cytokine release (especially tumor necrosis factor, interleukin- 1β , interleukin-6, and interleukin-18) from inflammatory cells.⁴¹ The $\alpha 7nAChRs$ 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.^{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-2.⁴³⁻⁴⁵ Alexandris *et al.* proposed that repurposing the approved drugs for smoking cessation and neurological conditions might be a therapeutic strategy in severe COVID-19.⁴⁶

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-19.⁴⁷ 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.^{48,49} Also, numerous studies have suggested that electrical or pharmacological potentiation of CAP through $\alpha 7nAChR$ activation, using vagus nerve stimulation devices or exogenous $\alpha 7nAChR$ agonists (such as nicotine or pharmacological compounds) could represent innovative therapeutic strategies to limit COVID-19-induced cytokine storm.^{50,51} Accumulated findings show that the inflammatory reflex drives a coordinated anti-inflammatory function, and show that its anti-inflammatory potential

FIGURE 1 The direct interaction of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with alpha-7 subtype of the nicotinic acetylcholine receptor ($\alpha 7nAChR$) and indirect effects of SARS-CoV-2 in inducing autonomic dysfunction might participate in the pathogenesis of coronavirus disease 2019. Regarding the protective role of the endogenous inflammatory reflex, these two pieces of evidence about the effects of SARS-CoV-2 are significant in designing an efficient therapeutic strategy against coronavirus disease 2019. NF- κ B



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 *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

TABLE 1 Different types, diagnostic methods, and range of complications of the nervous system in coronavirus disease 2019 infection

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.

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.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.⁵⁹ In that study, an interaction between the pentameric $\alpha 7nAChR$ and SARS-CoV-2 was observed.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.^{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.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.^{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.⁶⁵ In this regard, heart rate variability in the evaluation of autonomic balance might provide an important source of information in COVID-19.^{66–68} Mao *et al.* investigated the neurological manifestations of SARS-CoV-2 infection that were observed in almost 40% of the infected patients.⁶⁹ Blood–brain barrier breakdown as a potential mechanism of SARS-CoV-2-induced neurological dysfunction was proposed in some studies.^{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.^{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 improve pulmonary function in an animal model of lung injury.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.⁷⁵

The neurological manifestations of COVID-19 and autonomic dysfunction after COVID-19 infection were highlighted in some early-stage experiments.^{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.^{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.⁶⁰

Many efforts have been made to study the possibility of developing and using early immunological and non-invasive ANS-neuroimmunological biomarkers that would be better suited to economically diagnose, and ideally predict, COVID-19 outcome. Thus, some specific consequences and comorbidities associated with COVID-19 infection that are related to autonomic dysfunction can be prevented by inflammatory reflex stimulation.⁸⁰ However, detailed insights into the connection between vagal tone, autonomic dysfunction and the severity of

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.⁸¹ Here, we highlighted the autonomic dysfunction as a non-respiratory symptom in COVID-19 infection and point 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 $\alpha 7$ nAChR and autonomic dysfunction – both of which are caused by SARS-CoV-2 infection. This virus could interact with $\alpha 7$ nAChR, 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.⁸²

Knowledge of $\alpha 7$ nAChR 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 $\alpha 7$ nAChR inhibition by SARS-CoV-2 and neurological symptoms are two important features of SARS-CoV-2 infection. We suggest that activation of $\alpha 7$ nAChR by vagus nerve stimulation (e.g. electrical or pharmacological) or perhaps $\alpha 7$ nAChR 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 $\alpha 7$ nAChR functions or dysregulation of the ANS plays a key role in the pathophysiology of COVID-19.

ACKNOWLEDGMENTS

The authors thank the staff of the Immunology Research Center of Tabriz University of Medical Sciences for their sincere collaboration and support.

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.

ORCID

Khalil Hajiasgharzadeh  <https://orcid.org/0000-0003-4593-4803>

Mahdi Jafarlou  <https://orcid.org/0000-0003-0162-5937>

Behzad Mansoori  <https://orcid.org/0000-0001-9444-7134>

Narges Dastmalchi  <https://orcid.org/0000-0003-3391-4274>

Behzad Baradaran  <https://orcid.org/0000-0002-8642-6795>

Alireza Khabbazi  <https://orcid.org/0000-0002-9482-6967>

REFERENCES

- Lotfinejad P, Asadzadeh Z, Najjary S, Somi MH, Hajiasgharzadeh K, Mokhtarzadeh A, et al. COVID-19 infection: concise review based on the immunological perspective. *Immunol Invest.* 2020;51:246–65.
- Pum A, Ennemoser M, Adage T, Kungl AJ. Cytokines and chemokines in SARS-CoV-2 infections—therapeutic strategies targeting cytokine storm. *Biomolecules.* 2021;11(1):91.
- Al-Doorri A, Ahmed D, Kadhom M, Yousif E. Herbal medicine as an alternative method to treat and prevent COVID-19. *Baghdad J Biochem Appl Biol Sci.* 2021;2(01):1–20.
- Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodríguez L. SARS-CoV-2 infection: the role of cytokines in COVID-19 disease. *Cytokine Growth Factor Rev.* 2020;54:62–75.
- Lahav E, Rosenboim M, Shahrabani S, Song Y. Optimism and precautionary measures during the COVID-19 outbreak in China. *Am J Health Behav.* 2021;45(6):978–92.
- Vitiello A, Ferrara F. Colchicine and SARS-CoV-2: management of the hyperinflammatory state. *Respir Med.* 2021;178:106322.
- De La Flor JC, Valga F, Marschall A, Monzon T, Albarracín C, Ruiz E, et al. Targeting cytokine storm in COVID-19: a role of online Hemodiafiltration with asymmetric cellulose triacetate in maintenance hemodialysis patients—A report of 10 cases. *Case Reports Nephrol.* 2021;2021:1–7.
- Ahmed F. A network-based analysis reveals the mechanism underlying vitamin D in suppressing cytokine storm and virus in SARS-CoV-2 infection. *Front Immunol.* 2020;11:3084.
- Weaver RH, Jackson A, Lanigan J, Power TG, Anderson A, Cox AE, et al. Health behaviors at the onset of the COVID-19 pandemic. *Am J Health Behav.* 2021;45(1):44–61.
- Tracey KJ. Physiology and immunology of the cholinergic antiinflammatory pathway. *J Clin Invest.* 2007;117(2):289–96.
- Hajiasgharzadeh K, Baradaran B, Aghebati Maleki L, Khabbazi A. Nicotinic acetylcholine receptors as potential tumor biomarkers in genitourinary cancers: a review study. *ImmunoAnalysis.* 2021;1(1):4–4.
- De Jaco A, Bernardini L, Rosati J, Tata AM. Alpha-7 nicotinic receptors in nervous system disorders: from function to therapeutic perspectives. *Cent Nerv Syst Agents Med Chem.* 2017;17(2):100–8.
- De Rosa MJ, Esandi MDC, Garelli A, Rayes D, Bouzat C. Relationship between $\alpha 7$ nAChR and apoptosis in human lymphocytes. *J Neuroimmunol.* 2005;160(1–2):154–61.
- Yoshikawa H, Kurokawa M, Ozaki N, Nara K, Atou K, Takada E, et al. Nicotine inhibits the production of proinflammatory mediators in human monocytes by suppression of I- κ B phosphorylation and nuclear factor- κ B transcriptional activity through nicotinic acetylcholine receptor $\kappa 7$. *Clin Exp Immunol.* 2006 Oct;146(1):116–23.
- de Jonge WJ, van der Zanden EP, The FO, Bijlsma MF, van Westerloo DJ, Bennink RJ, et al. Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. *Nat Immunol.* 2005;6(8):844–51.

16. Rezonzew G, Chumley P, Feng W, Hua P, Siegal GP, Jaimes EA. Nicotine exposure and the progression of chronic kidney disease: role of the $\alpha 7$ -nicotinic acetylcholine receptor. *Am J Physiol Physiol*. 2012; 303(2):F304–12.
17. Suzuki S, Cohen SM, Arnold LL, Kato H, Fuji S, Pennington KL, et al. Orally administered nicotine effects on rat urinary bladder proliferation and carcinogenesis. *Toxicology*. 2018;398–399:31–40.
18. Qi J, Xue W, Zhang Y, Qu C, Lu B, Yin Y, et al. Cholinergic $\alpha 5$ nicotinic receptor is involved in the proliferation and invasion of human prostate cancer cells. *Oncol Rep*. 2019;43:159–68.
19. Zhang Q, Pei L, Liu M, Lv F, Chen G, Wang H. Reduced testicular steroidogenesis in rat offspring by prenatal nicotine exposure: epigenetic programming and heritability via nAChR/HDAC4. *Food Chem Toxicol*. 2020;135:111057.
20. Faghir-Ghanesefat H, Rahimi N, Yarmohammadi F, Mokhtari T, Abdollahi AR, Ejtemaei Mehr S, et al. The expression, localization and function of $\alpha 7$ nicotinic acetylcholine receptor in rat corpus cavernosum. *J Pharm Pharmacol*. 2017;69(12):1754–61.
21. Wang C, Gu W, Zhang Y, Ji Y, Wen Y, Xu X. Nicotine promotes cervical carcinoma cell line HeLa migration and invasion by activating PI3k/Akt/NF- κ B pathway in vitro. *Exp Toxicol Pathol*. 2017;69(6): 402–7.
22. Harmacych SJ, Kumar J, Bouni ME, Chadee DN. Nicotine inhibits MAPK signaling and spheroid invasion in ovarian cancer cells. *Exp Cell Res*. 2020;394(1):112167.
23. Wu Y, Wang L-P, Pan J-Q. Nicotinic acetylcholine receptor agonists may be a novel therapy for endometriosis. *Med Hypotheses*. 2011; 77(5):745–7.
24. Tu CC, Huang CY, Cheng WL, Hung CS, Chang YJ, Wei PL. Silencing A7-nAChR levels increases the sensitivity of gastric cancer cells to ixabepilone treatment. *Tumor Biol*. 2016;37(7):9493–501.
25. Wong HPS, Yu L, Lam EK, Tai EKK, Wu WKK, Cho CH. Nicotine promotes cell proliferation via $\alpha 7$ -nicotinic acetylcholine receptor and catecholamine-synthesizing enzymes-mediated pathway in human colon adenocarcinoma HT-29 cells. *Toxicol Appl Pharmacol*. 2007; 221(3):261–7.
26. Al-Wadei MH, Al-Wadei HAN, Schuller HM. Pancreatic cancer cells and Normal pancreatic duct epithelial cells express an autocrine catecholamine loop that is activated by nicotinic acetylcholine receptors 3, 5, and 7. *Mol Cancer Res*. 2012;10(2):239–49.
27. Zhang L, Wu LL, Huan HB, Chen XJ, Wen XD, Yang DP, et al. Sympathetic and parasympathetic innervation in hepatocellular carcinoma. *Neoplasma*. 2017;64(06):840–6.
28. Hajiasgharzadeh K, Sadigh-Eteghad S, Mansoori B, Mokhtarzadeh A, Shanehbandi D, Doustvandi MA, Asadzadeh Z, Baradaran B Alpha7 nicotinic acetylcholine receptors in lung inflammation and carcinogenesis: friends or foes? *J Cell Physiol* 2019;234(January):14666–79.
29. Gauthier AG, Lin M, Wu J, Kennedy TP, Daley L-A, Ashby CR, et al. From nicotine to the cholinergic anti-inflammatory reflex – can nicotine alleviate the dysregulated inflammation in COVID-19? *J Immunotoxicol*. 2021;18(1):23–9.
30. Lallai V, Manca L, Fowler CD. E-cigarette vape and lung ACE2 expression: implications for coronavirus vulnerability. *Environ Toxicol Pharmacol*. 2021;86:103656.
31. Wang Q, Sundar IK, Li D, Lucas JH, Muthumalage T, McDonough SR, et al. E-cigarette-induced pulmonary inflammation and dysregulated repair are mediated by nAChR $\alpha 7$ receptor: role of nAChR $\alpha 7$ in SARS-CoV-2 Covid-19 ACE2 receptor regulation. *Respir Res*. 2020; 21(1):154.
32. Koopman FA, Chavan SS, Miljko S, Grazio S, Sokolovic S, Schuurman PR, et al. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. *Proc Natl Acad Sci*. 2016;113(29):8284–9.
33. Bonaz B, Sinniger V, Hoffmann D, Clarençon D, Mathieu N, Dantzer C, et al. Chronic vagus nerve stimulation in Crohn's disease: a 6-month follow-up pilot study. *Neurogastroenterol Motil*. 2016;28(6): 948–53.
34. Occhinegro A, Wong CY, Chua BY, Jackson DC, McKinley MJ, McAllen RM, et al. The endogenous inflammatory reflex inhibits the inflammatory response to different immune challenges in mice. *Brain Behav Immun*. 2021;97:371–5.
35. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature*. 2000;405(6785):458–62.
36. Tracey KJ. The inflammatory reflex. *Nature*. 2002;420(6917):853–9.
37. Andersson U, Tracey KJ. Reflex principles of immunological homeostasis. *Annu Rev Immunol*. 2012;30(1):313–35.
38. Martelli D, Farmer DGS, McKinley MJ, Yao ST, McAllen RM. Anti-inflammatory reflex action of splanchnic sympathetic nerves is distributed across abdominal organs. *Am J Physiol Integr Comp Physiol*. 2019;316(3):R235–42.
39. Chavan SS, Pavlov VA, Tracey KJ. Mechanisms and therapeutic relevance of neuro-immune communication. *Immunity*. 2017;46(6): 927–42.
40. Pavlov VA, Tracey KJ. Neural regulation of immunity: molecular mechanisms and clinical translation. *Nat Neurosci*. 2017;20(2): 156–66.
41. Wang HH, Yu M, Ochani M, Amella CA, Tanovic M, Susarla S, et al. Nicotinic acetylcholine receptor $\alpha 7$ subunit is an essential regulator of inflammation. *Nature*. 2003;421(6921):384–8.
42. Skok MV, Grailhe R, Agenes F, Changeux J-P. The role of nicotinic receptors in B-lymphocyte development and activation. *Life Sci*. 2007;80(24–25):2334–6.
43. Changeux J-P, Amoura Z, Rey FA, Miyara M. A nicotinic hypothesis for Covid-19 with preventive and therapeutic implications. *Comptes Rendus Biol*. 2020;343(1):33–9.
44. Tizabi Y, Getachew B, Copeland RL, Aschner M. Nicotine and the nicotinic cholinergic system in COVID-19. *FEBS J*. 2020;287(17): 3656–63.
45. Kloc M, Ghobrial RM, Kubiak JZ. How nicotine can inhibit cytokine storm in the lungs and prevent or lessen the severity of COVID-19 infection? *Immunol Lett*. 2020;224:28–9.
46. Alexandris N, Lagoumintzis G, Chasapis CT, Leonidas DD, Papadopoulos GE, Tzartos SJ, et al. Nicotinic cholinergic system and COVID-19: in silico evaluation of nicotinic acetylcholine receptor agonists as potential therapeutic interventions. *Toxicol Reports*. 2021;8:73–83.
47. Bonaz B, Sinniger V, Pellissier S. Targeting the cholinergic anti-inflammatory pathway with vagus nerve stimulation in patients with Covid-19? *Bioelectron Med*. 2020;6(1):15.
48. Kaniusas E, Szeles JC, Kampusch S, Alfageme-Lopez N, Yucuma-Conde D, Li X, et al. Non-invasive auricular Vagus nerve stimulation as a potential treatment for Covid19-originated acute respiratory distress syndrome. *Front Physiol*. 2020;11:890.
49. Li S, Qi D, Li J, Deng X, Wang D. Vagus nerve stimulation enhances the cholinergic anti-inflammatory pathway to reduce lung injury in acute respiratory distress syndrome via STAT3. *Cell Death Discov*. 2021;7(1):63.
50. Farsalinos K, Niaura R, Le Houezec J, Barbouni A, Tsatsakis A, Kouretas D, et al. Editorial: nicotine and SARS-CoV-2: COVID-19 may be a disease of the nicotinic cholinergic system. *Toxicol Rep*. 2020;7:658–63.
51. Gonzalez-Rubio J, Navarro-Lopez C, Lopez-Najera E, Lopez-Najera A, Jimenez-Diaz L, Navarro-Lopez JD, et al. Cytokine release syndrome (CRS) and nicotine in COVID-19 patients: trying to calm the storm. *Front Immunol*. 2020;11. <https://doi.org/10.3389/fimmu.2020.01359>.
52. Li R-T, Qin C-F. Expression pattern and function of SARS-CoV-2 receptor ACE2. *Biosaf Heal*. 2021;3:312–8.
53. Suleiman A, Rafaa T, Al-rawi A, Dawood M. The impact of ACE2 genetic polymorphisms (rs2106809 and rs2074192) on gender

- susceptibility to COVID-19 infection and recovery: a systematic review. *Baghdad J Biochem Appl Biol Sci.* 2021;2(03):167–80.
54. Dormoy V, Perotin J-M, Gosset P, Maskos U, Polette M, Deslée G. Nicotinic receptors as SARS-CoV-2 spike co-receptors? *Med Hypotheses.* 2022;158:110741.
 55. Tanmay S, Labrou D, Farsalinos K, Poulas K. Is SARS-CoV-2 spike glycoprotein impairing macrophage function via $\alpha 7$ -nicotinic acetylcholine receptors? *Food Chem Toxicol.* 2021;152:112184.
 56. Han X, Li W, Li P, Zheng Z, Lin B, Zhou B, et al. Stimulation of $\alpha 7$ nicotinic acetylcholine receptor by nicotine suppresses Decidual M1 macrophage polarization against inflammation in lipopolysaccharide-induced preeclampsia-like mouse model. *Front Immunol.* 2021;12:1275.
 57. Yang J, Lai Y, Chen J, Lin B, Zhou B, Han X. Changes in alpha-7 nicotinic acetylcholine receptor and macrophage polarization state participate in the regulation of cervical remodeling in pregnant rats†. *Biol Reprod.* 2019;101:950–60.
 58. Lagoumintzis G, Chasapis CT, Alexandris N, Kouretas D, Tzartos S, Eliopoulos E, et al. Nicotinic cholinergic system and COVID-19: in silico identification of interactions between $\alpha 7$ nicotinic acetylcholine receptor and the cryptic epitopes of SARS-co-V and SARS-CoV-2 spike glycoproteins. *Food Chem Toxicol.* 2021;149:112009.
 59. Farsalinos K, Eliopoulos E, Leonidas DD, Papadopoulos GE, Tzartos S, Poulas K. Nicotinic cholinergic system and COVID-19: in silico identification of an interaction between SARS-CoV-2 and nicotinic receptors with potential therapeutic targeting implications. *Int J Mol Sci.* 2020;21(16):5807.
 60. Buoite Stella A, Furlanis G, Frezza NA, Valentinotti R, Ajcevic M, Manganotti P. Autonomic dysfunction in post-COVID patients with and without neurological symptoms: a prospective multidomain observational study. *J Neurol.* 2021;269:587–96.
 61. Shams Vahdati S, Ala A, Rahmanpour D, Sadeghi-Hokmabadi E, Tahmasbi F. Neurological manifestations of COVID-19 infection: an umbrella review. *Egypt J Neurol Psychiatry Neurosurg.* 2021;57(1):113.
 62. Guilmot A, Maldonado S, Sellimi A, Bronchain M, Hanseeuw B, Belkhir L, et al. Immune-mediated neurological syndromes in SARS-CoV-2-infected patients. *J Neurol.* 2021;268(3):751–7.
 63. Porzionato A, Emmi A, Barbon S, Boscolo-Berto R, Stecco C, Stocco E, et al. Sympathetic activation: a potential link between comorbidities and COVID-19. *FEBS J.* 2020;287(17):3681–8.
 64. Barizien N, Le Guen M, Russel S, Touche P, Huang F, Vallée A. Clinical characterization of dysautonomia in long COVID-19 patients. *Sci Rep.* 2021;11(1):14042.
 65. Kanberg N, Ashton NJ, Andersson L-M, Yilmaz A, Lindh M, Nilsson S, et al. Neurochemical evidence of astrocytic and neuronal injury commonly found in COVID-19. *Neurology.* 2020;95(12):e1754–9.
 66. Bourdillon N, Yazdani S, Schmitt L, Millet GP. Effects of COVID-19 lockdown on heart rate variability. *Boulossa D, editor. PLoS One.* 2020;15(11):e0242303.
 67. Junarta J, Riley JM, Pavri BB. Describing heart rate variability in patients with chronic atrial fibrillation during hospitalization for COVID-19. *J Arrhythmia.* 2021;37(4):893–8.
 68. Hajiasgharzadeh K, Baradaran B. Cholinergic anti-inflammatory pathway and the liver. *Adv Pharm Bull.* 2017;7(4):507–13.
 69. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 2020;77(6):683–90.
 70. Balcom EF, Nath A, Power C. Acute and chronic neurological disorders in COVID-19: potential mechanisms of disease. *Brain.* 2021;144:3576–88.
 71. Yarlagadda A, Preston SL, Jeyadhas RP, Lang AE, Hammamieh R, Clayton AH. Blood-brain barrier: COVID-19, pandemics, and cytokine norms. *Innov Clin Neurosci.* 2021;18(1–3):21–3.
 72. Platt MP, Bolding KA, Wayne CR, Chaudhry S, Cutforth T, Franks KM, et al. Th17 lymphocytes drive vascular and neuronal deficits in a mouse model of postinfectious autoimmune encephalitis. *Proc Natl Acad Sci.* 2020;117(12):6708–16.
 73. Abdoli Shadbad M, Hajiasgharzadeh K, Baradaran B. Cross-talk between myeloid-derived suppressor cells and Mucin1 in breast cancer vaccination: on the verge of a breakthrough. *Life Sci.* 2020;258:118128.
 74. Liu Y, Tao T, Li W, Bo Y. Regulating autonomic nervous system homeostasis improves pulmonary function in rabbits with acute lung injury. *BMC Pulm Med.* 2017;17(1):98.
 75. Abrams RMC, Simpson DM, Navis A, Jette N, Zhou L, Shin SC. Small fiber neuropathy associated with SARS-CoV-2 infection. *Muscle Nerve.* 2022;65(4):440–3.
 76. Shouman K, Vanichkachorn G, Cheshire WP, Suarez MD, Shelly S, Lamotte GJ, et al. Autonomic dysfunction following COVID-19 infection: an early experience. *Clin Auton Res.* 2021;31(3):385–94.
 77. Goodman BP, Khoury JA, Blair JE, Grill MF. COVID-19 Dysautonomia. *Front Neurol.* 2021;12:543.
 78. Johansson A, Mohamed MS, Moulin TC, Schiöth HB. Neurological manifestations of COVID-19: a comprehensive literature review and discussion of mechanisms. *J Neuroimmunol.* 2021;358:577658.
 79. Becker RC. Autonomic dysfunction in SARS-COV-2 infection acute and long-term implications COVID-19 editor's page series. *J Thromb Thrombolysis.* 2021;52:692–707.
 80. Reyes-Lagos JJ, Abarca-Castro EA, Echeverría JC, Mendieta-Zerón H, Vargas-Caraveo A, Pacheco-López G. A translational perspective of maternal immune activation by SARS-CoV-2 on the potential prenatal origin of neurodevelopmental disorders: the role of the cholinergic anti-inflammatory pathway. *Front Psychol.* 2021;12:708.
 81. Halpert G, Amital H, Shoenfeld Y. Dysregulation of G protein-coupled receptors of the autonomic nervous system, adrenergic and muscarinic acetylcholine receptors, in patients with autoimmune dysautonomic-related disorders. *Brain, Behav Immun - Heal.* 2020;4:100056.
 82. Courties A, Boussier J, Hadjadj J, Yatim N, Barnabei L, Péré H, et al. Regulation of the acetylcholine/ $\alpha 7$ nAChR anti-inflammatory pathway in COVID-19 patients. *Sci Rep.* 2021;11(1):11886.
 83. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ.* 2020;368:m1091.
 84. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med.* 2020;382(23):2268–70.
 85. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020;191:145–7.
 86. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol.* 2020;5(3):279–84.
 87. Goldberg MF, Goldberg MF, Cerejo R, Tayal AH. Cerebrovascular Disease in COVID-19. *Am J Neuroradiol.* 2020;41(7):1170–2.
 88. Lu L, Xiong W, Liu D, Liu J, Yang D, Li N, et al. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: a retrospective multicenter study. *Epilepsia.* 2020;61(6):e49–53.

How to cite this article: Hajiasgharzadeh K, Jafarlou M, Mansoori B, Dastmalchi N, Baradaran B, Khabbazi A. Inflammatory reflex disruption in COVID-19. *Clin Exp Neuroimmunol.* 2022. <https://doi.org/10.1111/cen3.12703>