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VIEWPOINT

Nicotine and the nicotinic cholinergic system in COVID-19

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There is an urgent need to address the devastating pandemic, COVID-19, caused by SARS-CoV-2. The efforts to understand the details of this disease in hope of providing effective treatments are commendable. It is clear now that the virus can cause far more damage in patients with comorbid conditions—particularly in those with respiratory, cardiovascular, or immune-compromised system—than in patients without such comorbidities. Drug use can further exacerbate the condition. In this regard, the ill effects of smoking are amply documented, and no doubt can be a confounding factor in COVID-19 progression. Although conflicting hypotheses on the potential role of nicotine in COVID-19 pathology have recently been offered, we believe that nicotine itself, through its interaction with the nicotinic cholinergic system, as well as ACE2, may not only be of use in a variety of neuropsychiatric and neurodegenerative diseases, but may also be of potential use in COVID-19. Thus, on one hand, while we strongly support smoking cessation as a means of harm reduction associated with COVID-19, on the other hand, we support a potential therapeutic role for nicotine, nicotinic agonists, or positive allosteric modulators of nicotinic cholinergic receptors in COVID-19, owing to their varied effects including mood regulation, anti-inflammatory, and purported interference with SARS-CoV-2 entry and/or replication.

Introduction

The worldwide toll exacted by a single-stranded RNA virus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), leading to the coronavirus disease of 2019 (COVID-19), is a wake-up call to better understand the role of viruses and infectious elements and to come up with an improved strategy for collective responses to pandemics.

It is quite evident that COVID-19 pathologies discriminately involve patients with underlying diseases such as hypertension, cardiovascular and cerebrovascular diseases, diabetes, hepatitis B infections, chronic obstructive pulmonary disease, chronic kidney diseases, malignancy, and immunodeficiency *vs.* those without such conditions. Expectedly, having two or more comorbidities further escalates the risks of succumbing to COVID-19 [1–3].

COVID-19 could also be hitting hard some populations with substance use disorders (SUDs) owing to the fact that people who use tobacco or marijuana or those with opioid or methamphetamine use disorders may have compromised respiratory and pulmonary health [4]. Similarly, alcohol use disorder (AUD), by impairing the immune system and increasing susceptibility to respiratory illnesses, could contribute to

Abbreviations
ACh, acetylcholine; ACE2, angiotensin-converting enzyme 2; ANG-(1–7), angiotensin 1-7; ARDS, acute respiratory distress syndrome; AUD, alcohol use disorder; CCL2, chemokine L2; CNS, central nervous system; COVID-19, coronavirus disease of 2019; IL, interleukin; nAChRs, nicotinic cholinergic receptors; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SUD, substance use disorder.

greater mortality risk when combined with COVID-19 [5]. There is, however, considerable controversy regarding the interaction of the plant alkaloid nicotine with COVID-19.

Nicotinic cholinergic receptors

Nicotinic cholinergic receptors (nAChRs), target of nicotine, belong to ionotropic class of receptors, which act by directly regulating the opening of a cation channel in the neuronal membrane [6–8]. Various subtypes of these receptors with distinct anatomical, physiological, and pharmacological characteristics have been identified [6]. Although nAChRs are present at the neuromuscular junction, autonomic ganglia, and the central nervous system, the subunit structures of these receptors are different from each other [9]. Considerable information on interaction between neuronal nicotinic receptors, consisting mainly of alph4-beta2 or homomeric alpha7 subunits and other neurotransmitter systems, is now available. Moreover, specific responses of these receptors to nicotine and their involvement in cognitive functions have been investigated [10,11]. Indeed, therapeutic potentials for selective nicotinic receptor agonists in various neuropsychiatric and neurodegenerative disorders have been suggested. These include Parkinson's disease and Alzheimer's disease, schizophrenia, depression, pain, and smoking cessation [12–15]. The potential role of nicotinic receptors in high-order cognitive processing has been recently reviewed [16].

nAChRs and inflammation

It is also of relevance that acetylcholine (ACh), both centrally and peripherally, acts not only through the nicotinic, but also through the muscarinic receptors, which are G protein-coupled receptors and act via the second messenger system. Our emphasis here is solely on the ionotropic nicotinic receptors that act directly on channel opening. It is now believed that there exists a cholinergic anti-inflammatory pathway that acts through nicotinic acetylcholine receptors [17,18]. Thus, activation of these receptors (particularly α7 nAChR) can suppress production of pro-inflammatory cytokines as these receptors are abundantly expressed in variety of immune cells including B cells, T cells, and macrophages [19]. Indeed, nicotine has been shown to inhibit pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-6 without affecting the anti-inflammatory cytokines such as IL-10 [20,21]. Interestingly, several animal models associated with elevated levels of pro-inflammatory cytokines such as sepsis, ischemia–reperfusion, and pancreatitis show improvement by stimulation of the vagus nerve, which is believed to be mediated via activation of α7 nAChRs on macrophages [22]. Moreover, mice deficient in α7 nAChRs exhibit increased endotoxin-induced TNF-α production, which do not respond to electrical vagal stimulation [22]. Thus, it may be concluded that nicotine—via α7 nAChR stimulation—might lead to inhibition of cytokine storm associated with COVID-19 described further below. Importantly, nicotine use has been advocated in diseases associated with immune dysregulation (autoimmune diseases) or various inflammatory diseases such as multiple sclerosis, type 1 diabetes, rheumatoid arthritis, and inflammatory bowel diseases [23–25].

Smoking, nicotine, and COVID-19

Substantial evidence indicates adverse effects of smoking on COVID-19 including predisposition to the virus infection, severity of progression, and mortality [1,26,27,28,29]. However, there is a meta-analysis report that concludes that active smoking is not associated with severity of coronavirus disease [30], although this contention has been challenged [26]. Still, some studies claim to have found a lower incidence of hospitalized COVID-19 patients among smokers [31,32].

However, the evidence accumulated up to now suggests that although smokers might be less hospitalized, their health risk increases as soon as they are hospitalized [33]. Thus, it seems prudent to indicate that smoking is a risk factor for COVID-19 given the overwhelming epidemiological evidence cited above. However, the relationship of the stimulant in cigarettes, nicotine, with COVID-19 is far from clear. Thus, some investigators argue that because of known nicotinic receptor interactions with angiotensin-converting enzyme 2 (ACE2), a channel for SARS-CoV-2 entry into cells, nicotine exposure can increase the risk for COVID-19 damage, including neuroinfection [34]. Moreover, it was reported that exposure to nicotine causes epithelial cells to increase ACE2 levels, whereas gene silencing of α7 nAChR appears to significantly dampen this response [35], leading to the suggestion that perhaps α7 nAChR-selective antagonists, by altering ACE2 expression, may prevent SARS-CoV-2 entry into the airway epithelium [36]. These contentions, however, stand in stark contrast with potential beneficial effects of nicotine or nicotinic agonists in a variety of diseases [13,37], including COVID-19 [18,19,38].

Part of these discrepancies might stem from the way of interpreting studies; for example, some of the

conclusions on the impact of smoking on COVID-19 are inferred, rather than directly analyzed [1,31]. Another possible reason for the discrepancies might lie in the attempt to predict the final outcome of a drug based on its presumptive mode of action [38,39]. Interaction of nicotine with ACE2 appears to be far more complicated to allow a definite prediction of the entry of the SARS-CoV-2 into the epithelium. This is due to the fact that not only our full understanding of the role of ACE2 in general, and in COVID-19 in particular, is incomplete, but also our knowledge of interaction between nicotine and ACE2 is far from clear [38–41]. Thus, although it is believed that SARS-CoV-2 uses ACE2 as a receptor for cell entry, involvement of other receptors cannot be totally ruled out [38,41,42,43,44]. Moreover, SARS-CoV-2 has been reported to either downregulate [45–47] or upregulate ACE2 [28,36,48]. In this regard, it is important to note that ACE2 polymorphism, which could influence both the susceptibility of people to SARS-CoV-2 infection and the outcome of the COVID-19, was recently described in human populations [40,45]. Importantly, it has been hypothesized that increased ACE2 levels may actually be beneficial rather than harmful, particularly in patients with lung injury as it has been shown to have potent vasodilatory, anti-inflammatory, and antioxidant properties [49–51]. Interestingly, children and younger adults, who have milder COVID-19 symptoms, have higher ACE2 levels compared to older people [52].

Smoking, nicotine, and ACE2

On one hand, it is proposed that smoking or nicotine may upregulate the detrimental angiotensin-converting enzyme (ACE) but downregulate the compensatory ACE2/ANG-(1–7) receptor axis and hence contribute to cardiovascular and pulmonary diseases [53–55]. On the other hand, nicotine, via activation of α7 nAChR exposure, may actually increase ACE2 levels in the epithelial cells [36]. This latter effect, consistent with the observations of several other investigators [55,56], would jive with the hypothesis proposed by Vaduganathan et al [51] and elaborated above and would support potential beneficial effects of nicotine in countering COVID-19. It must be emphasized that the action of nicotine *per se* should be distinguished from thousands of other chemicals in tobacco or even e-cigarettes [57] that are known to be harmful to the body. Indeed, smoking is also a significant risk factor for mortality due to infections of various respiratory viruses including seasonal influenza as well as potential progression of COVID-19 [1,27,28,29,33]. However, nicotine or nicotinic agonists, as discussed above, may have significant therapeutic potentials including COVID-19 [37,38,51,58].

nAChRs and cytokine storm

The postulated mechanism for the efficacy of nicotine in infectious diseases in general, and in COVID-19 in particular, includes restoring and re-activating the cholinergic anti-inflammatory pathway that can suppress the cytokine storm, also referred to as macrophage activation syndrome [18,59]. Cytokine storm, a dangerous hyperinflammatory state associated with elevated levels of several pro-inflammatory cytokines, such as IL-1β, IL-2, IL-6, IL-17, IL-8, TNF-α, and chemokine L2 (CCL2), has been observed in COVID-19 patients and appears to be the hallmark of severe cases [60–62]. For this reason, treatment with anti-IL-6 anti-TNF-α medications have been proposed and clinical trials are already underway [63,64]. However, restoring and re-activating the cholinergic anti-inflammatory pathway may be far more beneficial than administering inhibitors of a single cytokine [31,38,58]. Animal studies also show that nicotine, by reducing leukocyte infiltration and pro-inflammatory mediators in bronchoalveolar lavage fluid, has protective effects against lipopolysaccharide-induced acute respiratory distress syndrome (ARDS) [65,66]. Thus, as recently advocated by González-Rubio and colleagues, use of nicotine or nicotinic agonists may also be effective in ameliorating cytokine storm by inhibiting several cytokines simultaneously [18].

COVID-19—nAChRs—CNS

It is of interest to note that SARS-CoV-2 may enter the central nervous system (CNS) through the bloodstream, via the olfactory nerve across the cribriform plate, by disrupting the blood–brain barrier (BBB) or infecting the peripheral nerves [43,67,68,69], where it may cause ACE2 downregulation and a local inflammatory response referred to as neuroinvasion, a common feature of coronaviruses [70]. Indeed, COVID-19 has been shown to be associated with the CNS and neurological effects (e.g., dizziness, headache, confusion, agitation, anxiety, depression, strokes, seizures, and loss of smell and taste) [71,72]. A recent report indicates that neurological complications may be manifested in more than half of hospitalized COVID-19 patients [73].

The established anti-inflammatory effects of nicotine, together with its capability to improve olfactory impairment in a mouse model of Parkinson's disease

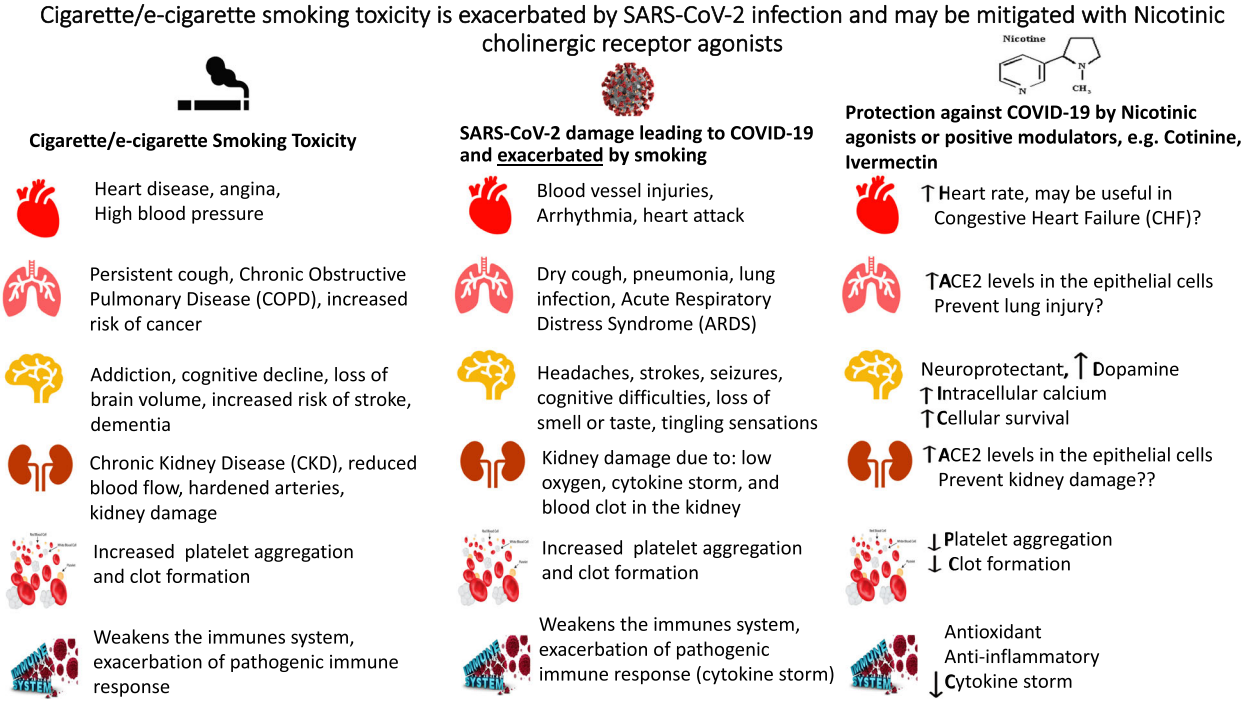

Fig. 1. Detrimental effects of cigarette/e-cigarette smoking and exacerbation of these effects with SARS-CoV-2 infection in columns 1 and 2, respectively. Column 3 depicts potential therapeutic intervention by nicotinic agonists or positive allosteric modulators in COVID-19.

[74], provide further credence to its potential usefulness in COVID-19, as loss of smell is also a common symptom of COVID-19 [75]. Moreover, nicotine might counter some of the neurological effects of COVID-19, not only because of its anti-inflammatory, but also because of its neuroprotectant and mood improvement properties [13–15]. Indeed, it has been proposed that COVID-19 may be a disease of the cholinergic nicotinic system [76]. Hence, nicotine administration could be added on top of antiviral or other therapeutic options for COVID-19. This application is very feasible as various pharmaceutical nicotine products such as nicotine patch, gum, nasal spray, and inhaler are already available and FDA-approved for smoking cessation. Additionally, while some cytokine inhibitors are associated with elevated risk of opportunistic infections [77], no such effect has been attributed to pure nicotine [78]. In this regard, it is noteworthy that the mode of nicotine administration has to be carefully considered as the pharmacokinetic and pharmacodynamic of different nicotinic preparation can be significantly different [79]. Recently, it has also been proposed that positive allosteric modulators of the α7 nAChRs may be used to boost nicotine's effects in countering excessive inflammation caused by SARS-CoV-2 [80]. Interestingly, ivermectin, a positive allosteric modulator of α7 nAChR [81], has been shown to inhibit the replication of SARS-CoV-2 in cells *in vitro* [82]. Hence, it may be suggested that a combination of nicotine and ivermectin might be a reasonable pharmacotherapy in COVID-19. In the same vein, it should be noted that cotinine, a metabolite of nicotine, but without its addictive properties, has been shown to have similar anti-inflammatory effects as nicotine and hence cotinine or selective nAChR agonists or even varenicline, a partial alpha4-beta2 agonist used for smoking cessation may be potential substitutes for nicotine [83,84].

COVID-19—nAChRs—coagulation

Finally, another prominent feature of COVID-19 is coagulopathy that results in thromboembolic complications, which are associated with higher mortality rate [85,86]. Interestingly, platelets express functional α7 nAChRs, deficiency of which may increase platelet activity and increase the chance of clot formation [87]. Since acetylcholine may act as an endogenous inhibitor of platelet activation [88], it would be of significant interest to examine whether nicotine or selective nAChR agonists may also affect COVID-19-induced coagulopathy. In this regard, it is of interest to note

that whereas extracts of electronic cigarettes can enhance platelet adhesion potential toward fibrinogen, pure nicotine may actually inhibit platelet function [89].

In summary, detrimental effects of smoking on general health and aggravation of viral infections should be a serious consideration for quitting smoking. On the other hand, nicotine, nicotinic receptor agonists, or positive modulators of these receptors may be of therapeutic potential in a variety of diseases including countering at least some of the harms of COVID-19 (Fig. 1).

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

YT, BG, MA, and RLC conceived and wrote the paper. YT and BG provided the figure.

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