

Review article

Smoke, Nicotine, Opioids, and Cannabinoids Effects on the ACE2 Protein Level and Possibility of COVID-19 Infection: Suggesting Potential Preventives and Therapeutics

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SUMMARY

Introduction. The coronavirus caused the pandemic COVID-19 that has an extensive influence in the world. The virus enters and infects body cells through superficial protein ACE2. Each cell possessing ACE2 is potentially vulnerable to this virus. Since the respiratory system is exposed to the environment and has ACE2, it is one of the first candidates infected by the virus. One of the considerable complications in the severe stage of COVID-19 is an intense adaptive immunological response that is detrimental to body organs.

Methods. This is a review article. All relevant articles which were accessible were reviewed.

Results. Some drugs of abuse may have an adverse or beneficial influence on the disease, and their simultaneity with COVID-19 is remarkable. Nicotine and cholinergic nicotinic receptor agonists seem to decrease the cell's membrane superficial ACE2 protein number; thus, they would be appropriate candidates for COVID-19 prevention and expansion. Both opioids and cannabinoids attenuate the immune system and seem to be adverse for disease incidence but can be beneficial for the severe stage of COVID-19. The antitussive effect of some opioids would be advantageous. Furthermore, some opioids are substrates for ACE2 and they bind it. Therefore, they would be an appropriate candidate to design a drug covering ACE2 with a high affinity to prevent coronavirus infection.

Conclusion. Some drugs, such as nicotine and opioids, may have beneficial effects on preventing or reducing COVID-19 complications.

Keywords: COVID-19, ACE2, nicotine, opioid, cannabinoid, immune system, coronavirus

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INTRODUCTION

The coronavirus disease in 2019 (COVID-19) became a pandemic that infected many people around the world and became the major problem of global public health now (1). Therefore, the efforts made to find the ways to prevent and treat the disease are ongoing. Due to the similarity between COVID-19 (2019-nCoV) and severe acute respiratory syndrome (SARS), the method of dealing with COVID-19 has been estimated based on SARS (1).

The SARS-COV2 virus infects cells through binding the membrane superficial protein angiotensin-converting enzyme type 2 (ACE2) (2). Thus each part of the body that possesses ACE2 is vulnerable to COVID-19. At least in some patients, severe immunological complications occur that may be harmful (3). Therefore, the present article tries to present preventive and treatment methods according to ACE2 and/or immune system modulation through smoking, cholinergic nicotinic receptor, opioids, and cannabinoids.

METHODS

The present article was prepared according to the "Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P)" (4). The authors searched for all related published papers in PubMed, ScienceDirect, and also Google scholar. COVID-19, coronavirus, ACE2, smoking, cigarette, nicotine, opioid, cannabinoid, and related words were the keywords in the searching procedures. We tried to use all related articles in English. The authors have no bias in presenting and analyzing the articles.

SMOKING

Tobacco smoke is a combination of more than 5,000 identified components. Tobacco smoking potentially produces free radicals and oxidative damages to the lung (5). Lung physiological responses following smoking include alveolar edema, surfactant deficiency, inflammation, and alveolar collapse (6). These conditions can cause chronic obstructive pulmonary disease (COPD) and emphysema (7). Eventually, the efficient respiratory area and lung efficiency have been reduced.

Plenty of studies have mentioned that cigarettes and smoking are detrimental to COVID-19 patients (8 - 10). In a study in China, 137 persons out of 1,085 COVID-19 patients were current smokers (12.6%), and 21 out of 1,085 were ex-smokers. In other words, 14.5 % of all patients were smokers in some period of life, and only 12.6% of all patients were current smokers (11). Another study showed that the number of smokers in China was much higher than this; 27.7 % of all adult Chinese and 52.1% of Chinese men were smokers in 2017 (12). Considering that 58.1 % of COVID-19 patients were Chinese men (11), the prevalence of the disease among smokers was lower; nevertheless, the severity of the disease was higher in current smokers than never-smokers (11). In another report, 2 out of 24 patients (8.3%) had a history of smoking (13). One report from Wuhan mentioned that 11 patients out of 191 were current smokers (5.7%), of which five patients died (14), so it can be concluded that smoking is a risk factor for death from COVID-19. Another report from Wuhan mentioned that three patients out of 41 were current smokers (7.3%) in which none of them needed ICU care (15). The other one reported that two patients out of 52 were smokers (3.8%), and they all survived (16). A study claimed that "age- and sex-matched comparisons indicate that mortality and symptom severity are higher in smokers and former smokers" (10); however, when one reads the reference, it would be clear that it does not claim that (17). Therefore, there are contradictory and sometimes unreliable findings. However, it seems that smoking is one of the risk factors for COVID-19 progression (18) and not for the incidence (Table 1).

In Iran, the average cigarette smoking prevalence is about 11 to 21% in adults (19, 20), but the total prevalence of smokers seems to be more. According to the information from COVID-19 patients admitted to hospitals affiliated to Babol University of Medical Sciences, the rate of smokers was lower, and 87 (7%) patients out of 1,248 adult patients were smokers (unpublished data).

Smoking induces epithelial changes, including epithelial cell proliferation and squamous cell metaplasia in the segmental bronchus (21). Hence membrane peptides content such as ACE2 may change (Figure 1A). ACE2 is a part of the renin-angiotensin system (RAS) more abundantly expressed on the

Table 1. Studies reporting the number of smoker and nonsmoker COVID-19 patients

Study	Country	Smokers' percentage (%)	Total COVID-19 patients	COVID-19 smoker patients number	COVID-19 smoker patients' percentage (%)
Fu et al. 2020	China	>27.7*	1085	137	12.6
Hu et al. 2020	China	>27.7*	24	2	8.3
Zhou et al. 2020	China	>27.7*	191	11	5.7
Huang et al. 2020	China	>27.7*	41	3	7.3
Yang et al. 2020	China	>27.7*	52	2	3.8
Present study	Iran	16**	1248	87	7

* According to Parascandola and Xiao, 2019

** According to Moosazadeh et al. 2013 and Mohammadian et al. 2018.

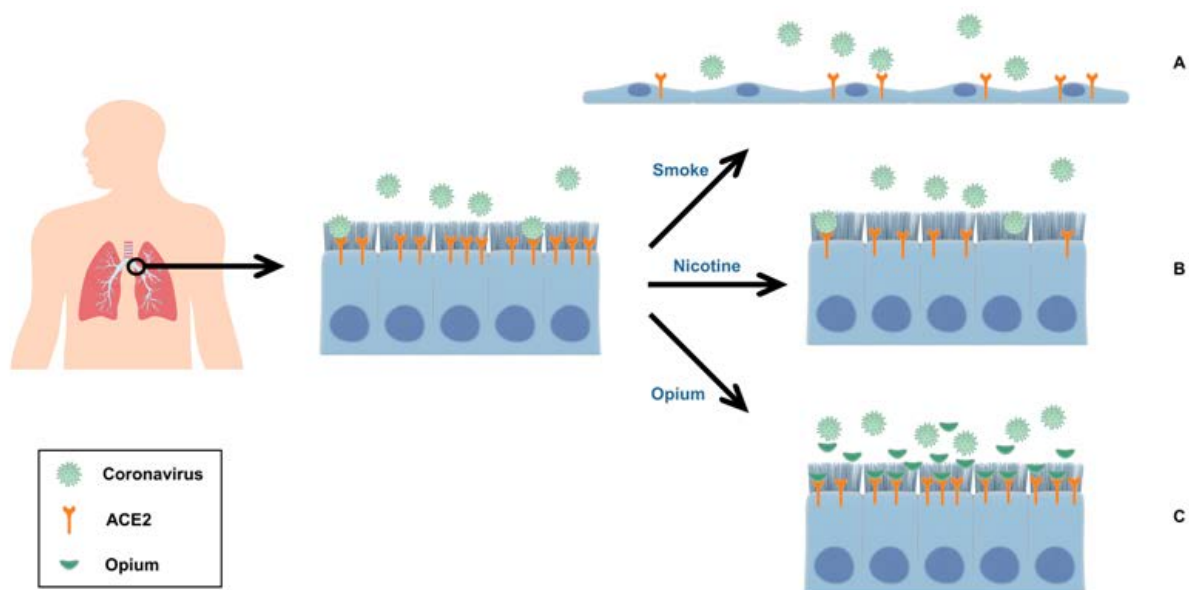


Figure 1. A schematic figure representing the lung, respiratory tracts, respiratory epithelium, ACE2, and coronavirus. **A:** shows the effect of smoke on the columnar respiratory epithelium that changes them to the squamous epithelial cells with probably lower ACE2. **B:** shows the nicotine and nicotinic cholinergic receptor agonists' effect on the ACE2 protein level on the surface of epithelial cells. **C:** shows that opioids can bind the superficial ACE2 and prevent the coronavirus binding. ACE2: angiotensin-converting enzyme type 2.

Table 2. Studies demonstrating cigarette smoke and nicotine effect on ACE2

Study	Treatment	Result	Location
Cai, 2020	Cigarette smoke	Higher ACE2 gene expression (mRNA)	Lung tissue
Smith et al. 2020	Cigarette smoke	Higher ACE2 gene expression and protein level	Respiratory tract goblet cells and not epithelium
Brake et al. 2020	Cigarette smoke	ACE2 upregulation	Type-2 pneumocytes and alveolar macrophages and not airways
Chappel M, Ferrario, 2006, Koka et al. 2008	Ang II/AT ₁ R activation	ACE2 downregulation	General
Kitamura, 1987	Cigarette smoke	CE activity and Ang II increase	Lung
Sugiyama, 1986	Cigarette smoke/ i.v. nicotine	CE activity and Ang II increase	Serum
Ferrari et al. 2007	Nicotine	Lower ACE2 protein level	Cultured neurons and glial cells

apical surface of well-differentiated polarized epithelial cells. Thus, SARS-COVID virus entry and leaving occurs primarily and preferentially from well-differentiated ciliated epithelial cells expressing ACE2 (22).

On the other hand, there are opposing reports (Table 2) as it was mentioned that Asian current smokers compared to non-smokers displayed higher ACE2 gene expression according to RNA sequencing, while other ethnicities and populations had no difference between smokers and non-smokers (23). Another study also confirmed cigarette smoke-induced ACE2 expression and protein level increase in the respiratory tract due to the proliferation of secretory cells such as the goblet cells. They mentioned that since cigarette smoke is a combination of several thousand components, it is not possible to relate it to one substance (24); therefore, this phenomenon is not generalizable and would not be observed for all components of cigarette smoke. Furthermore, it is indicated that the ACE2 was up-regulated in type-2 pneumocytes and alveolar macrophages in smokers (25) and not in their airways. Since these parts of the respiratory system are not directly exposed to the outside air, and they receive diluted and slow inspiratory flow, they would not be as notable as airway epithelial cells in COVID-19 incidence.

Among human tissues, ACE2 is expressed more in the kidney, rectum, colon, ileum, testis, pancreas, placenta, heart, and gallbladder. Although

it may be mentioned that ACE2 expression in the respiratory tract is limited, with none or low levels of ACE2 expression in the lung and respiratory epithelia (26), the receptor expression by bronchial (22) and alveolar epithelial cells (25) have been reported.

NICOTINE

Perhaps more important than smoke is the nicotine; through smoking, the lung is the first organ that encounters nicotine. Many cell types in the lung express the nicotinic acetylcholine receptors, including bronchial lumen surrounding the epithelial cells, type II alveolar pneumocytes, and free alveolar macrophages (27).

It was indicated that nicotine through smoking cigarette (28) or nicotine intravenous infusion (29) increased the ACE activity leading to the conversion of Ang I to Ang II, resulting in Ang II increase in the lung and serum after exposure to cigarette smoke. AT₁R activation by Ang II downregulates ACE2 through ERK/MAPK signaling pathway (30).

In cultured neurons and glial cells, ACE2 protein levels were lower in spontaneous hypertensive rats (SHR) than Wistar Kyoto rats (WKR). Furthermore, nicotine decreased ACE2 protein levels in both groups; however, the response of SHR was more pronounced compared to WKR (Figure 1B) (31).

ACE2 cleaves a single residue of angiotensin I (Ang I) to generate Ang 1-9 and decreases Ang II, the RAS's main effector, to the vasodilator Ang 1 - 7 (32, 33). The blockade of increased RAS results in an enhanced response in the expression of ACE2. The increase in ACE2 is consistent with elevated levels of Ang-(1 - 7) following the AT1 receptor or ACE blockade (33).

In addition to nicotine, several drugs of abuse such as amphetamine, cocaine, and cannabinoids increase blood pressure (34), so they can potentially decrease the ACE2 expression.

COVID-19 AND THE IMMUNE SYSTEM

COVID-19 is divided into two phases immunologically: the first innate immune defense-based phase that is protective and the secondary acquired immunological response phase such as inflammation and damaging. It seems that the early intrinsic immune response phase should be augmented, while the second detrimental phase should be suppressed. Thus, an efficient immune system may not benefit patients progressing to the severe stage (3).

Several drugs of abuse, including opioids and cannabinoids, seem to modulate the immune system. Amphetamine derivatives have a contradictory influence on the immune system (34). The same was seen for nicotine and smoking (35, 36).

OPIOIDS

Opioids can modulate the immune system directly and indirectly. The immune system cells express different types of opioid receptors, including μ , κ , δ , and non-classical opioid-like receptors (37); therefore, opioids can directly modulate the immune system. On the other hand, it was demonstrated that morphine increases serum glucocorticoids (38). As a result, opioids modulate the immune system indirectly, too.

Opioids suppress the production of IFN- γ by cultured human peripheral blood mononuclear cells (39).

Chronic opioids consumption was also shown to suppress macrophage progenitor cell proliferation (40). They inhibit the phagocytic activity of macrophages and neutrophils (37).

It was reported that morphine regulated the gene expression of α and β chemokines. Morphine treatment exhibited significant downregulation of IL-8 gene expression. Similarly, treatment with morphine suppressed the macrophage-inflammatory protein-1 β (MIP-1 β) gene expression (41).

Daily morphine doses suppressed peripheral blood mononuclear cell (PBMC) and natural killer (NK) cell activity and decreased the number of subpopulation effector cells, CD8+CD16+ (42).

Morphine administration decreased blood leukocyte expression of the main histocompatibility complex class II (MHC II RT1.B beta) and related molecules, including the MHC II invariant chain mostly on B lymphocytes surface (43).

Chronic morphine treatment suppressed cytotoxic T lymphocyte (CTL)- mediated cytolysis and granulation (44).

Direct exposure to opioids instantly inhibits chemotactic activities of monocytes and neutrophils toward the chemokines IL-8, MIP-1 β , RANTES (regulated upon activation, normal T cell expressed) (45), MIP-1 α , and monocyte chemoattractant protein-1 (MCP-1) (46). The same suppression was observed for microglial migration toward C5a (47).

Some opioids, such as codeine, can be used as an antitussive drug (48, 49) to decrease the COVID-19 induced coughs. Also, these opioids can bind to ACE2 with a suitable affinity (50). Soluble human ACE2 can hydrolyze some opioid peptides such as dynorphin A 1-13, β -casomorphin, and neocasomorphin to inactive fragments (51). Hence, they can be used to make null substrates binding to the ACE2 as a cover or even changing its spatial configuration so that the coronavirus would not identify and bind it (Figure 1C). Also, analgesic and sedative effects of opioids (52) can be beneficial for treating COVID-19 complications (Figure 2). Albeit, the respiratory depression caused by opioids (53) must be considered.

Opioids and cannabinoids interact in their actions in different aspects, such as the reward system (54 - 57) and the immune system. The immune system has both CB1 and CB2 receptors (58). The μ -opioid and CB1 receptors make a heterodimer structure (μ -CB1) in which both take effect through Gi-protein and each one mimics the other one's behavior (59). Therefore, the cannabinoids would have the same effects as opioids.

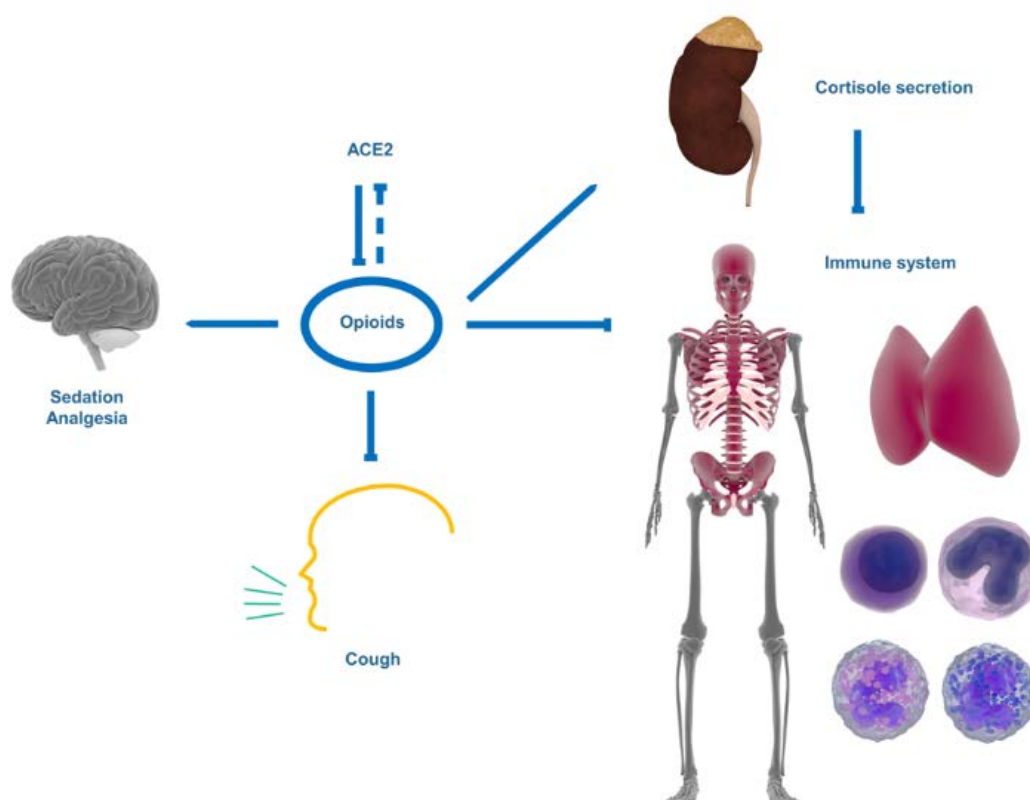


Figure 2. The possible beneficial and applied effects of opioids in COVID-19. ACE2: angiotensin-converting enzyme type 2. Lines with blocked ends display the inhibition. Block-ended dashed line represents possible blockage

CANNABINOIDS

The same as opioids, cannabinoids influence the immune system both directly and indirectly, directly via its CB1 and CB2 receptors (58) and indirectly via cortisol. Cannabinoids increase the plasma cortisol levels dose-dependently (60).

Various cannabinoids have been shown to suppress the functional activities of B lymphocytes, T lymphocytes, macrophages, and NK cells both *in vitro* and *in vivo* (61). Cannabinoid treatment significantly decreased the number of human IFN- γ producing cells and immune function (62). Cannabinoids result in suppressing immunity, early IFN- γ , IL-12, and IL-12 receptor beta 2 (63).

SUGGESTIONS

Nicotine, opium, and cannabinoids are potential therapeutics for COVID-19 complications. By

designing cholinergic nicotinic receptor agonists which act locally without detrimental side effects, they may decrease the superficial ACE2 protein level and prevent the COVID-19 infection or the progression of the disease and decrease its complications. Opioids can be used for designing a high-affinity null ligand binding to ACE2 in order to mask it and make it out of access. For patients with the severe phase of the disease, designing opioid and cannabinoid receptor agonists with an emphasis on immune system suppression would be beneficial. Furthermore, opioids sedative and antitussive effects would be helpful.

CONCLUSION

Cholinergic nicotinic receptor activation would lead to lower ACE2 receptor expression and,

accordingly, lower COVID-19 infection chance. Some drugs of abuse such as amphetamine, cocaine, and cannabinoids may do this by increasing the blood pressure. Opioids and cannabinoids via attenuating and suppressing the immune system may be helpful in the severe stage of COVID-19.

Acknowledgment

The authors would like to thank Dr. Mousa Mohammadnia-Afrouzi and Dr. Mehdi Shahbazi for their kind helping in figure preparation and data collecting, respectively. The present study received no funding.

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Uticaj duvanskog dima, nikotina, opioda i kanabinoida na nivo ACE2 proteina i mogućnost infekcije korona virusom: predlaganje potencijalnih preventivnih i terapijskih sredstava

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SAŽETAK

Uvod. Korona virus izazvao je pandemiju kovida 19, koja je ostavila snažan uticaj na ceo svet. Virus ulazi u organizam i pritom inficira ćelije kroz površinski protein ACE2. Svaka ćelija koja poseduje ACE2 protein potencijalno je osetljiva na virus. S obzirom na to da je respiratorni sistem izložen spoljašnjoj sredini i poseduje ACE2 protein, među prvima je na udaru ovog virusa. Jedna od značajnih komplikacija u teškoj fazi kovida 19 je intenzivan adaptivni imunološki odgovor koji deluje štetno na organizam.

Metode. Ovo je pregledni rad. Pregledani su svi relevantni radovi koji su bili dostupni.

Rezultati. Neke opojne supstance mogu da imaju nepoželjne ili povoljne efekte na samu bolest i njihovo konzumiranje u toku bolesti ima značajan uticaj na organizam. Izgleda da holinergički agonisti nikotinskog receptora smanjuju broj površinskih proteina ACE2 u ćelijskoj membrani. Na ovaj način oni bi predstavljali odgovarajuće kandidate za prevenciju širenja kovida 19. I opiodi i kanabinoidi oslabljuju imuni sistem i deluju štetno na organizam, ali mogu biti korisni kada je reč o težem stadijumu kovida 19. Antitusivni efekat nekih opioda bio bi povoljan. Štaviše, neki opiodi su supstrati za ACE2 i vezuju ga. Stoga bi oni bili odgovarajući kandidati za dizajniranje leka koji pokriva ACE2 sa visokim afinitetom za sprečavanje infekcije koronavirusom.

Zaključak. Neki lekovi, poput nikotina i opioda, mogu da imaju povoljne efekte na prevenciju ili smanjenje komplikacija izazvanih kovidom 19.

Ključne reči: kovid 19, ACE2, nikotin, opiod, kanabioid, imuni sistem, korona virus