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Covid-19, vagus nerve and phrenic nerve: three sides to the same story

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Abstract

This article aims to prove that there is an intoxication of the vagus and phrenic nerves in cases of covid 19 that lead to symptoms of the disease. First of all, it should be noted that the virus affects the nicotinic receptor a7(a7nAchR), which is the main arm of those peripheral nerves, thus paralyzing the function of both the respiratory system and that of the heart, which is controlled by those nerves. Through our analysis, we support that there is no case of Central Nervous System(CNS) entry, rather the Severe Acute Respiratory Coronavirus 2(SARS-CoV-2) can have distal effects on the CNS, through the microbiome and vagus nerve paralysis. Also, the Angiotensin Converting Enzyme 2(ACE2) receptor upregulation is the key to having milder symptoms. Last but not least, the administration of cholinergic agents, antiepileptics, or even vagus and phrenic nerve stimulation is proposed to be an effective treatment of covid-19.

Introduction:

1. Covid-19 and α7nAchR

The articles supporting the case of milder symptoms of covid 19, among smokers, claim that only a small percentage of smokers with covid-19, tend to be hospitalized, across the whole spectrum of ages.[1][2] They claim that nicotine has a protective role against covid-19, though no clinical trial has been performed, to verify this hypothesis. The reason for the low prevalence of covid 19 in the population of smokers, is hypothesized to be, the effects of nicotine. Nicotine is an nAchR full agonist, apart from the case of α9&α10 nAchRs, where it is considered to be an antagonist.[3] Thus, they concluded that an epitope in the spike protein of SARS-CoV-2 must interfere with nAchRs. The follow-up studies, identified an epitope, highly conserved across most coronaviruses, class B, in the sequence 375-390 of the spike of SARS-CoV-2.[4] Also, a high percentage of mutations take place across this epitope, so the researchers claim that probably, evolution favors changes within this conserved domain, due to the fact, that it offers an advantage of survival. Considering that most variants of SARS-CoV-2, carry mutations within this epitope, especially the 'Omicron' class variants, verifies that this offers an evolutionary advantage.[5] Through the in silico experiments with the spike of SARS-CoV-2, researchers managed to identify interactions with the α7nAchR, as well as the α9nAchR.[6] Note that nicotine is not administered in hospitalized patients, so any beneficial effects it may have against covid-19 quickly vanished. This

outcome is enhanced by the smoker's decision to quit smoking when diagnosed with covid-19. Those combined, 'verify' the claims of WHO that nicotine deteriorates covid-19. It's just that nicotine is not tested for its ability to combat the disease, thus it is removed from the equation, once the patient is diagnosed. The case of administering nicotine to hospitalized patients would be a good suggestion, to test its effects, which, before the illness, provided lower rates of infection or severe illness, among smokers, over the general population.[7]. However, nicotine should not be examined as a treatment solution, given its addiction.

2. The inflammatory reflex (CAP)

Having established the secondary receptor for intoxication, we should focus on the tissue, where this antagonism has the most detrimental effect. The inflammatory reflex is a known mechanism via which the immune system, communicates with the CNS and the vagus nerve. Its main arm is the α7nAchR, located both in neurons, as well as epithelial and immune system cells.[8] The antagonism of α7nAchR is detrimental to the CAP, since it disturbs the communication between the 3 factors, thus eliminating the reflex. The result of this is, in case of severe illness, a hyperinflammatory response, known as a cytokine storm.[9] A comparison of ARDS, mainly caused by the accumulation of pus in the alveoli, with the cytokine storm, shows major differences which support a possible link between the two.[10]
According to the authors mentioned above, the inflammatory reflex is vital for the establishment of covid-19. This of course is not significantly supported, other than the colleration between ARDS and cytokine storm. However, one might come to the same conclusion, having inspected the pharmacology of well-known vagus nerve inhibitors, that tend to paralyze the vagus nerve in high doses. One such example is the nicotinic antagonist pancuronium. Usually, when administered during anesthesia, it tends to stimulate the vagus nerve, but high doses have the opposite effect.[11] A link has been established between pancuronium and ARDS. It appears that the use of nondepolarizing neuromuscular blocking agents(NMBA) is not considered a therapeutic approach for ARDS and the same goes for pancuronium when used in high doses.[12] Even more, the citation above, supports that when pancuronium is used for the treatment of ARDS, monitoring the patient is vital for survival. More important than that, in low doses, pancuronium indicates hypoxia, ARDS, and other respiratory malfunctions, that require immediate transport to the ICUs.[11] Therefore, from the citations [11] and [12], we conclude that, probably, the use of NMBAs is not recommended in most cases, since the relaxation of skeletal muscles, often affects the vagus nerve as well. Pancuronium, due to its bipolar nature, in terms of pharmacology, is administered only in low doses and this proves that the inhibition of the vagus nerve, essentially deteriorates ARDS. This is evident both due to the reduction of oxygen volume inhaled and due to respiratory paralysis, caused by vagolytic effects. Respiratory paralysis is prolonged due to acidosis and hypokalemia[13] The most important aspect is that acidosis, mentioned above, is collerated with an increase in systemic inflammation.[14] Thus, we can safely assume that prolonged exposure to agents that have vagolytic effects, one of whom, is the spike of SARS-CoV-2, deteriorates the phenomenon of systemic inflammation. On the other hand, some antiepileptic medicine, such as valproic acid, lamotrigine, and carbamazepine, stimulate the vagus nerve and thus have the opposite effects.[15] In citation 14 that I listed, the authors noticed that a group of 269 patients, suffering from epilepsy, treated with antiepileptic drugs, without

modification of dose, for 1 year, showed a decrease in episodes, at first measured after a period of 3 months and then up to 12 months. This magnifies the importance of antiepileptic drugs when used as vagus nerve stimulators, which can be applied to covid-19 as well. Note that, epilepsy is associated with increased inflammation, which those medicines tend to reduce. The authors of the following citation suggest a hypothesis that the glia, referred to as non-neuronal cells, located in the brain, such as astrocytes, are important for inflammatory effects of epilepsy and are associated with the disease. Moreover, antiepileptic drugs, tend to affect those cells, thus reducing inflammation.[16] Thus antiepileptic drugs might be a useful therapy for severe cases of covid-19, given the crucial role that the vagus nerve has in the disease.

3. Viremia, CNS entry, and covid-19

Cytokine storm, mediated by vagus nerve paralysis, is amplified when there is also a case of viremia, which can damage various blood vessels and organs. Viremia is the term used to describe traces of the virus within blood vessels. There is extensive literature suggesting that viremia is a not-so-rare adverse effect of covid-19 and is associated with deteriorated progress of the disease.[17] It should be noted, however, that viremia is most commonly linked to RNAemia and not the virion itself. Such an example is the citation mentioned above. Note that another study shows that people suffering from covid-19 had suffered damage in the blood vessels of the CNS, despite having not traced the virus within the tissues of the brain. It should be noted however that these patients had a history of diabetes, and elderly age and were thus prone to severe symptoms.[18] Concerning the CNS entry, it should be addressed that the virus itself may be present in the blood, but does not cause signs of CNS infection. This suggests that any symptoms deriving from the CNS, such as insomnia, confusion, and stroke/brain bleeding, are included in the cardiovascular system's pathology. Any hypotheses of CNS entry, such as through the blood-brain barrier or the olfactory nerve, are validated only for the case of viremia, not CNS infection. The case of viremia is useful when studying the different organs, affected by the virus since mainly the liver and the kidneys are among the first to suffer. After all, this pinpoints us to the fact that child hepatitis has been hypothesized to be linked to previous (long covid) covid-19 infection.[19] All in all, CNS entry is restricted only to blood vessels in the brain and does not affect CNS neurons. Any changes noted in the phenotype, related to cognition or psychiatric disorders, must be attributed to altered blood supply in neuron cells. However, viremia is more important, because of the ability of the virus to affect multiple targets, through the blood. We suggest that a clinical trial be performed, to test whether a patient experiencing RNAemia, can transmit the disease to a healthy patient, through blood transfusion.

4. ACE2R upregulation as a protective measure against severe covid 19 infection

Some articles suggest that nicotine upregulates the ACE2(angiotensin 2 converting enzyme) receptor.[20] However, we have to disagree with the authors that this upregulation is detrimental. The most important aspect of this effect is the pharmacological perspective. The ACE2 does not have an intracellular pathway. Thus, it serves as a site for angiotensin 2, to be converted to angiotensin 1-7. If ACE2 receptors are few, then first the virus has fewer entry points to be replicated, but those that the spike binds to, cannot be used for angiotensin 2. Therefore, an increase in angiotensin 2 and thus

hypertension is expected to occur. On the other hand, the upregulation of ACE2 offers more sites for the angiotensin 2 to bind to, so there is no substantial change in blood pressure and thus no blood vessel damage, as mentioned in the cases of viremia. It is not the virus that damages the fibrinogen of the blood vessels, but cardiovascular complications, which amount to the majority of deaths from covid-19. Also, the renin-angiotensin system(RAS) is not disrupted and infected cells can subsequently respond to the infection, by producing interferons(IFNs) and other cytokines with anti-inflammatory effects[21], which are speculated to be extra effective against human coronaviruses![22]

5. Vagus nerve, mood, and microbiome

The vagus nerve is essential for controlling the microbiome and mood. Firstly, the link to the gastrointestinal system is established through the vagus nerve terminals on the enteric nervous system(ENS). The vagus nerve supports the Gut-Brain-Axis and helps with the communication between the two nervous systems. The hormones produced from the microbiome include glucagon-like peptide (GLP-1), peptide YY (PYY), cholecystokinin (CCK), corticotropin-releasing factor (CRF), oxytocin, and ghrelin. These hormones modulate anxiety and depression resembling symptoms that may occur via changes in the microbiome.[23] Supporting a toxicosis of the vagus nerve, and the subsequent symptom of diarrhea[24], may lead us to changes in the microbiome and essentially in mood disorders, often manifested as post-covid effects.[25] This, of course, must be co-attributed to the social isolation that occurred during the lockdowns, but the physiological parameter of this phenomenon is evident in the pathophysiology of the Gut-Brain-Axis.

6. Proof of vagus nerve intoxication

So far, we have claimed that the vagus nerve suffers the most, during a covid-19 infection. This is supported by the intoxication of the a7nAchR, which is the main arm of the vagus nerve, and also through mood disorders, that are associated with the Gut-Brain-Axis. But, the most promising result would be the proof of vagus nerve intoxication. Thus, we have to study the anatomy of the vagus nerve, compared to its proximity to the lungs, the main area of infection, due to SARS-CoV-2(Severe Acute Respiratory Coronavirus 2). Through the cited papers, we support that the vagus nerve communicates both with the heart, regulating heart rhythm,[26] and the lungs, regulating respiratory rhythm.[27] Concerning the lungs, the vagus nerve can modulate the immune system to combat infection and inflammation. Moreover, the case of immune evasion, through the lungs, might be caused by a paralysis of the vagus nerve, as supported in the case of covid 19, where the intoxication of M1 macrophages, in the lungs, leads to this phenomenon.[28][29] Of course, this is just a hypothesis, therefore, we have to co-align the immune evasion with the vagus nerve paralysis, which, so far has been connected mostly to reduced interferon(IFN) production[30] and the M1 macrophages I mentioned before. Given the dysregulation of the heart rhythm, often associated with atrial fibrillation and other types of arrythmia[31] and the case of ARDS(Acute Respiratory Distress Syndrome), which is a case of severe inflammation,[32] we can expect that the main mediator of those organs, is distorted. The articles we cited, mention that vagus nerve stimulation might be a possible treatment for ARDS. What is more important is that the phrenic nerve and the

vagus nerve both derive from the spine and are associated with different aspects of the respiratory system regulation, with the phrenic nerve, controlling breathing, which might be a key to the breathing difficulty that is noted in severe covid 19 cases.[33] Given that the phrenic nerve expresses nAchR receptors, mainly the a7nAchR, we can assume that it is also a target of the virus.[34]

Conclusion

The virus SARS-CoV-2 can affect all respiratory system cells that express the a7nAchR, referring to the M1 macrophages, the epithelial lung cells, the vagus nerve cells, and the phrenic nerve cells. To reverse this intoxication, we have to administer drugs that stimulate those peripheral nerves, the vagus, and the phrenic, either via direct stimulation or through the use of cholinergic agents. Nicotine might a good solution, but given its addictive nature, it can hardly lead to any benefits, in the long term, for the patient. Such medications could be many AchE inhibitors, such as physostigmine. Also, given their ability to enhance vagus nerve function, antiepileptic agents should be considered as well. Last but not least, an experiment should be performed, with the conduction of Positron Emission tomography(PET) in the lungs, both in mildly ill and severely ill, covid 19 patients, to detect any changes in the peripheral nerve function and therefore prove our point.

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