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Mini Review

Are "Sartans" the Common Treatment for COVID-19 and Parkinson's Disease?

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Abstract

COVID-19 disease is caused by the SARS-CoV-2 virus that, after originating in Wuhan, China, spread rapidly throughout the world. As this pathogen enters host cells through the angiotensin converting enzyme 2 protein, angiotensin II hydrolysis may be impaired, contributing to COVID-19 pathology. Indeed, angiotensin II serum levels have been positively corelated with both the SARS-CoV-2 viral load and the severity of lung injuries. Moreover, angiotensin II binding to its type 1 receptors has been associated with host immune dysfunction and the subsequent COVID-19 critical illness. On the other hand, disruption of this signaling pathway in the brain substantia nigra has been associated with Parkinson's disease, suggesting that SARS-CoV-2 infection may share a common pathophysiology with movement disorders. The connection between COVID-19 and Parkinson's disease is further supported by the fact that antiviral natural killer cells and cytotoxic T cells express both renin-angiotensin and dopamine systems that the virus can exploit for immune evasion.

In this perspective article, we look at angiotens in II receptor blockers, "sartans", alone or in combination with angiotens in (1-7) agonists, as potential treatment modalities for both COVID-19 and Parkinson's disease.

Keywords: Sartans; COVID-19; Delirium

Introduction

COVID-19 pandemic is caused by the SARS-CoV-2 virus that originated in China and spread rapidly around the globe, infecting, at the time of this writing, over 3 million people and causing more than 300,000 fatalities. It is believed that 40-50% of COVID-19 patients present with neuropsychiatric symptoms, including strokes, cognitive dysfunction, depression, psychosis and delirium, suggesting that SARS-CoV-2 may be a neurotropic virus [1-4]. Although, Parkinson's disease (PD) or secondary parkinsonism have not been described in association with COVID-19, movement disorders have accompanied prior pandemics, suggesting that they could follow [5,6].

SARS-CoV-2 enters host cells through the angiotensin converting enzyme 2 (ACE-2), likely impairing angiotensin II (ANG II) hydrolysis into angiotensin [1-7]. This may lead to the unopposed accumulation of ANG II and COVID-19 pathology. Indeed, several studies have associated ANG II serum levels with SARS-CoV-2 viral load and the severity of lung injuries [7-9]. In addition, ANGII activation of its type 1 receptors (AT-1Rs) was found to facilitate viral infection by disabling mitochondria-mediated immunity [10-12].

Aside from the traditional or circulating renin-angiotensin system (RAS), the brain and immune cells express a local RAS, essential for the integrity of antiviral defense and the substantia nigra (SN) dopaminergic neurons [13]. RAS homeostasis is maintained by balancing its two opposing branches, the vertical, with ANG II as its main representative, and the horizontal, comprised of angiotens in [1-7], alamandine and their receptors [14]. Together these pathways regulate the production of reactive oxygen species (ROS) and nitric oxide (NO), limiting the generation of toxic peroxynitrite [15]. When SARS-CoV-2 binds ACE-2, the horizontal RAS branch may be disabled, and the vertical enhanced, theoretically predisposing to both COVID-19 and parkinsonism (Figure 1). Indeed, the vertical branch inhibitors or angiotensin receptor blockers (ARBs) were found beneficial in PD animal models and are currently in clinical trials for COVID-19, suggesting therapeutic properties for both conditions [16-21] (NCT04335123)(NCT04312009)(NCT04311177). According to this model, ARBs combined with horizontal RAS agonists may completely reverse the SARS-CoV-2 immune suppression, ameliorating both the infectious and neuropsychiatric consequences of this virus.

COVID-19 and Angiotensin II

Numerous studies have connected COVID-19 pandemic with RAS and its component, ACE-2. As SARS-CoV-2 virus accesses host tissues via ACE-2 protein, it likely impairs ANG II hydrolysis, leading to the unopposed accumulation of this peptide. In addition, as RAS and ACE-2 are also expressed by the host immune cells, viral binding may disrupt immunity, predisposing to the COVID-19. Moreover, immune cells, including NK cells, also express a dopamine system (DAS) which interacts with RAS at the mitochondrial level, regulating antiviral responses [22,23]. Indeed, several earlier studies have shown that ANGII activation of its type 1 receptors (AT-1Rs) disrupts mitochondrial antiviral signaling (MAVS) proteins and the generation of type I interferon [10,12]. This is further supported by the studies that found a direct relationship between ANG II serum levels, SARS-CoV-2 viral load and the severity of lung injuries, linking this illness to mitochondria-mediated immunity [7-9].

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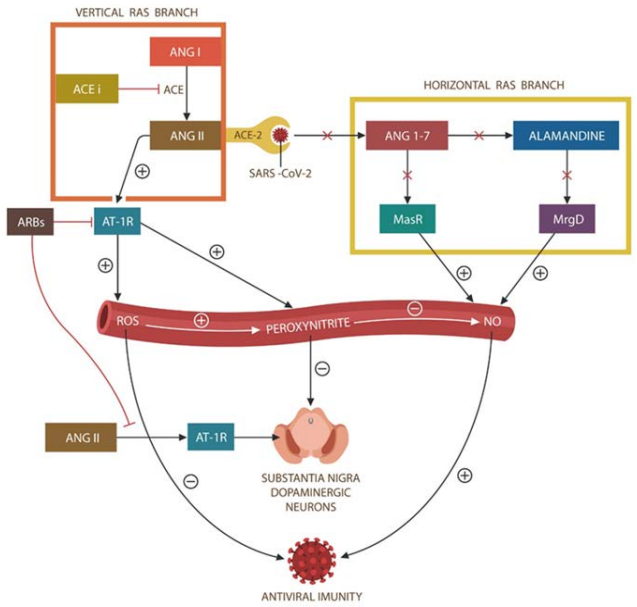

Figure 1: The vertical and horizontal RAS branches maintain redox homeostasis by regulating the generation of ROS and NO. ACE-2/SARS-CoV-2 binding disables the horizontal branch, disrupting the REDOX homeostasis with resultant NO depletion and upregulation of ROS and peroxynitrate. Since a local RAS is operational in immune cells and SN, the homeostasis of antiviral immunity and the dopaminergic neurons is impaired. ARBs block the vertical RAS pathway (although they do not affect the virus-blocked horizontal branch), rebalancing the system. Combining ARBs with ANG [1-7] agonists would likely reverse SARS-CoV-2 actions better than ARBs alone.

Aside from regulating the arterial blood pressure, RAS is essential for NO homeostasis, peroxynitrite down regulation and lowering the oxidative and nitrosative stress [24]. Indeed, novel data have indicated that, contrary to prior beliefs, NO is a potent antioxidant, neuroprotector and inhibitor of SARS-CoV-2 replication [25]. However, in the presence of excessive oxidation, NO engenders peroxynitrite, a toxin that promotes both viral infection and SN damage [24,26,27]. Indeed, SARS-CoV-2 virus may facilitate its own replication by generating excessive peroxynitrite and ROS as well as by depleting NO [28,29]. As a result of these findings, not only has the US Food and Drug Administration (FDA) expanded the use of NO in COVID-19 but is currently evaluating it for its overall antiviral properties [30] (NCT04388683).

Aside from the immune cells, RAS and ACE-2 are also expressed by the SN dopaminergic neurons, therefore movement disorders could follow SARS-CoV-2 infection [13]. Indeed, dysfunctional ANG II/AT-1R signaling in SN was reported in PD animal models, revealing the RAS and DAS interconnectedness in this disorder [31]. Along these lines, recent studies have found that excessive SN peroxynitrite impairs dopamine (DA) synthesis, likely contributing to parkinsonism [32-34]. Others have demonstrated a direct relationship between the serum peroxynitrite level and scoring on the unified Parkinson's disease rating scale (UPDRS), linking this disorder to RAS and DAS dysregulation [35,36].

RAS is comprised of two opposing pathways joined by the ANG II/ACE-2 interaction. The vertical branch, consisting of ANG II/AT-1Rs signaling, generates ROS which, aside from inducing oxidative stress, play a major signaling role [37]. The horizontal RAS branch, represented by ANG [1-7], alamandine and their respective receptors MasR and MrgD, generates NO, optimizing antiviral immunity and the homeostasis of SN dopaminergic neurons [38,39]. When SARS-CoV-2 binds ACE-2, the signaling in the vertical RAS branch may be enhanced, while the horizontal inhibited, favoring both viral infection and movement disorders (Figure 1).

Taken together, COVID-19 disrupts antiviral immunity by up regulating the vertical RAS and inhibiting the protective horizontal branch. This results in increased oxidative and nitrosative stress, peroxynitrite upregulation and lower NO, predisposing to COVID-19 and secondary parkinsonism [28].

Covid-19 and Cellular Senescence

Novel studies have connected the excessive activation of vertical RAS branch with p21-mediated cellular senescence in several tissues, including the brain, endothelia and immunity [40-42]. This is significant as a recent study reported that dopaminergic neurons in PD may not undergo apoptosis, as previously believed, but p21-induced cellular senescence [43,44]. As senescence may be potentially reversible, this is good news for patients with PD providing a safe modality for p21 inhibition.

Many studies have reported that viruses replicate more effectively in senescent cells and can induce this phenotype in host tissues [45-47]. For example, the H7N9 influenza virus triggers endothelial cell senescence to disrupt the blood-brain barrier (BBB) and enter the brain [48]. Other examples of virus-induced cellular senescence include the human immunodeficiency virus (HIV) and cytomegalovirus (CMV) that thrive by promoting host immune senescence [49]. To induce senescence and activate p21, viruses often attack mitochondria, releasing excessive ROS and mitochondrial DNA (mtDNA) [50]. Interestingly, PD was associated with abnormal "immune aging", involving NK cells and CD4 lymphocytes, linking senescence to the pathogenesis of this movement disorder [51-53]. Along these lines, a recent study has found that COVID-19 patients age and die prematurely, losing on average a decade in years of life lost (YLL), linking this virus to aging [54]. Moreover, since COVID-19 appears to target older individuals, this pathogen may promote premature senescence in addition to accelerating the normal aging process [55]. Taken together, this data is in line with prior findings, linking virus-induced senescence to neurodegenerative disorders [45,56,57].

A Fresh Look at Viral Parkinsonism

Viral parkinsonism is a topic closely related to cellular senescence as viruses were demonstrated to induce this phenotype in many cell types, including the neurons and lymphocytes, promoting neurodegeneration [58]. Primary PD is a progressive neurodegenerative disorder marked by motor and nonmotor symptoms, caused by an impairment of SN dopaminergic neurons [59]. Secondary parkinsonism or PD-like symptoms can be induced by numerous agents, including viral infections along with the oxidative or nitrosative stress triggered by these pathogens [60-62].

Many viruses, probably including SARS-CoV-2, are neurotropic and capable of inducing SN damage. Indeed, around half of COVID-19 patients, were found to experience DAS-related symptoms, including inattention, depression, psychosis and delirium [1-4]. Similar

neuropsychiatric manifestations were described following the 1918 influenza pandemic that may have caused encephalitis lethargica (EL), a condition marked by various central nervous system (CNS) symptoms, including movement disorders [63-65]. Contemporary cases of virus induced EL have been accompanied by secondary parkinsonism, linking viruses to DAS disruption [64]. Interestingly, viruses were demonstrated to lower immune responses by altering host DA levels which in return may induce parkinsonism [23,66]. For example, Japanese encephalitis virus (JEV) was shown to enter host cells via DA receptors and target SN, resulting in movement disorders [67]. Another example is HIV which lowers host immune responses by down regulating human dopamine transporters (hDATs), an action that often triggers parkinsonism [68,69]. The link between DA and immunity is further substantiated by the fact that PD patients treated with L-DOPA or DA agonists frequently develop immune adverse effects [70,71]. Interestingly, peroxynitrate was found to inhibit hDAT, suggesting that SARS-CoV-2-upregulation of this toxin may suppress immunity [72,73]. Indeed, as low hDAT levels characterize PD, COVID-19 peroxynitrite upregulation may lower these proteins further, exacerbating SN damage [74]. On the other hand, DA blockers, including chlorpromazine, have been demonstrated to augment host antiviral immunity and were proposed as COVID-19 treatments [75-77] (NCT04366739). As a result of these findings, we speculate that patients taking antipsychotic medications may be somewhat protected against SARS-CoV-2 infection as suggested by the emerging research on forensic inpatients (unpublished data). Additionally, methamphetamine (METH) use disorder has been associated with both PD and impaired immunity, linking this drug to COVID-19 vulnerability (see the next section).

Are NK Cells the Missing Link between COVID-19 and PD?

NK cells are innate immune lymphocytes that play a major role in clearing malignant, virus-infected and senescent cells, preventing their accumulation and disease progression [78]. These lymphocytes, expressing both RAS and DAS, maintain the integrity of both antiviral immunity and the SN dopaminergic neurons [22,40,78,79]. Lately, NK cells have been under intense scrutiny by the research community as their dysfunction was associated with viral infections, cancer and PD [80]. Indeed, it was recently reported that, under normal circumstances, NK cells lower the progression of PD by clearing α-synuclein [81]. Others have reported an inverse relationship between α-synuclein and hDATs in NK cells and SN, emphasizing the role of these transporters in antiviral immunity and the SN integrity [82]. As hDATs regulate the extra and intracellular DA levels, viral exploitation of these proteins may lower immune responses and predispose to PD. Indeed, as human NK cells express higher levels of DA receptors compared to other immune cells, they are more susceptible to viral manipulation [23]. Indeed, earlier studies have reported that up regulated DA inhibits NK cell function via the immune checkpoint, NKG2A [79]. A recent study found that SARS-CoV-2 can disrupt NK cells DAS by up regulating NKG2A [83]. For this reason, active NK cells are currently in clinical trials for COVID-19 (NCT04324996) (NCT04375176). Furthermore, a sunder normal circumstances, NK cells also function to eliminate senescent cells, they may directly link PD to p21-induced cellular senescence [10,43]. Indeed, it has been reported that senescent cells over expressing NKG2A immune checkpoint are resistant to NK cells elimination, associating once more viruses with senescence [83,84]. The NK cells RAS and DAS and their link to antiviral immunity and PD is further supported by methamphetamine (METH) studies. Several reports have been published, linking chronic METH exposure to lower NK cells number and function, suggesting that users may beat higher risk of both PD and COVID-19 illness [85-89]. Indeed, METH-upregulated peroxinitrite and hDAT downregulation were reported to exacerbate movement disorders [87,88]. Interestingly, like COVID-19, METH was demonstrated to augment ANG II/AT-1R signaling, linking DA to vertical RAS activation [90]. Moreover, preclinical studies have reported that candesartan treatment decreases METH self-administration, linking RAS and DAS and indicating that this ARB may be the drug of choice for COVID-19 METH users [91]. Furthermore, aside from directly inhibiting hDAT, METH may promote PD indirectly by disrupting the function of NK cells leading to α-synuclein accumulation [92-95].

Several studies have connected METH with mitochondrial disruption and susceptibility to COVID-19, suggesting once more the centrality of these organelles in antiviral immunity [96-98]. Indeed, under normal circumstances, viral RNA activates mitochondrial MAVS (via RIG-1), inducing the synthesis of type type 1 interferon to eliminate the virus (Figure 2) [99]. With the same token, α-synuclein accumulation may predispose to COVID-19 by impairing NK cells [100].

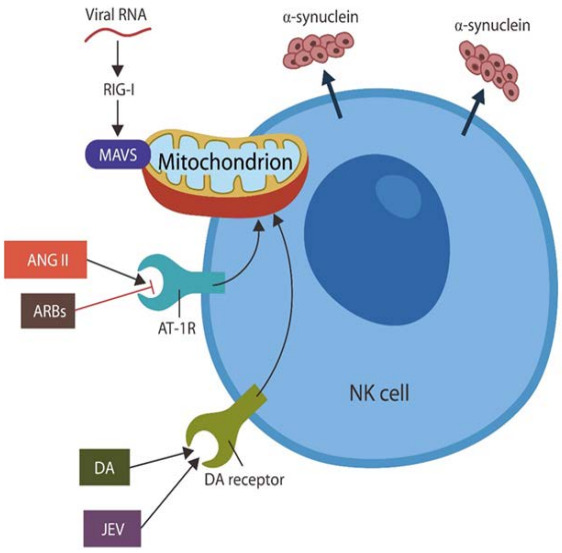

Figure 2: Natural killer cells play a crucial role in both COVID-19 (by eliminating virus-infected cells) and PD (by clearing α-synuclein). Since these lymphocytes express both RAS and DAS their disruption alters mitochondrial function, impairing antiviral immunity. Under physiological circumstances, SARS-CoV-2 RNA activates mitochondrial MAVS (via RIG-1), promoting the synthesis of type 1 interferon (not shown). The unopposed activation of the vertical RAS branch induces mitochondrial damage via ANG II. This action is inhibited by ARBs. DAS overactivation by viruses, including JAV and possibly SARS-CoV-2, disrupts the mitochondrion. This action is blocked by DA blockers, such as chlorpromazine.

Taken together, this data suggests that ARBs may benefit both COVID-19 and PD patients as these agents may augment immunity and protect SN. Moreover, adding ANG [1-7] agonists may optimize the antiviral and PD treatment by reactivating the horizontal RAS branch.

Conclusion

Severe illness and neuropsychiatric manifestations associated with COVID-19 may have a common denominator: Over activation of the vertical RAS branch and blocking the horizontal. Excess generation of ANG II and peroxynitrite likely disrupts the RAS and DAS in both NK cells and SN, damaging antiviral immunity and the dopaminergic neurons.

This model predicts both, that movement sequelae may follow COVID-19 and that "sartans", alone or in combination with ANG [1-7] agonists, could be therapeutic for both.

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