REVIEW ARTICLE

Potential implications of angiotensin-converting enzyme 2 blockades on neuroinflammation in SARS-CoV-2 infection

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Abstract:

Background: Angiotensin-converting enzyme 2 (ACE2) has been reported as a portal for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Consequently, scientific strategies to combat coronavirus disease of 2019 (COVID-19) were targeted to arrest SARS-CoV-2 invasion by blocking ACE2. While blocking ACE2 appears a beneficial approach to treat COVID-19, clinical concerns have been raised primarily due to the various intrinsic roles of ACE2 in neurological functions. Selective reports indicate that angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) upregulate ACE2 levels. ACE2 metabolizes angiotensin II and several peptides, including apelin-13, neurotensin, kinetensin, dynorphin, [des-Arg9] bradykinin, and [Lys-des-Arg9]-bradykinin, which may elicit neuroprotective effects. Since ARBs and ACEIs upregulate ACE2, it may be hypothesized that patients with hypertension receiving ARBs and ACEIs may have higher expression of ACE2 and thus be at a greater risk of severe disease from the SARS-CoV-2 infections. However, recent clinical reports indicate the beneficial role of ARBs/ACEIs in reducing COVID-19 severity. Together, this warrants a further study of the effects of ACE2 blockades in hypertensive patients medicated with ARBs/ACEIs, and their consequential impact on neuronal health. However, the associations between their blockade and any neuroinflammation also warrant further research.

Objective: This review collates mechanistic insights into the dichotomous roles of ACE2 in SARS-CoV-2 invasion and neurometabolic functions and the possible impact of ACE2 blockade on neuroinflammation.

Conclusion: It has been concluded that ACE2 blockade imposes neuroinflammation.

Keywords: COVID-19, SARS-CoV-2, angiotensin-converting enzyme 2, neuroinflammation, hypertension.

1. INTRODUCTION

The coronavirus disease of 2019 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is undoubtedly the worst pandemic of its kind. Its prevalence shook the world, with 117,799,584 cases worldwide and a global death toll rising to 2,615,018 as of 11th March 2021 [1]. Furthermore, SARS-CoV-2 has been reported to demonstrate higher virulence than the previous strain, SARS-CoV. This is due to an alteration in several amino acid residues of SARS-CoV-2, which favors enhanced hydrophobic interactions and salt bridge formation [2]. Hence, several strategies to combat SARS-CoV-2 are currently under scientific investigation, including preventing viral invasion to the host cell by blocking the port of entry. SARS-CoV-2 internalization is mediated by host cell-derived transmembrane protease serine 2 (TMPRSS2), which helps in the priming of the viral spike protein and facilitates its-

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-interaction with a membrane-bound form of angiotensin-converting enzyme 2 (ACE2), sometimes referred to as the ACE2 receptor [3]. Once SARS-CoV-2 binds with ACE2, it undergoes endocytosis to enter the endosomal compartments, which is cathepsin-L dependent [4] and then finally escapes into the cytoplasm. Later, SARS-CoV-2 releases the RNA genome to initiate its replication and assembly in the cytoplasm [5]. Thus, blocking ACE2 has been regarded as a potential drug target against SARS-CoV-2 invasion. Paradoxically, ACE2 has been well considered for its beneficial role in neurological health outcomes [6,7,8]. Hence, several clinical concerns arise when treating COVID-19 patients with ACE2 blockers, as it may trigger neuroinflammation. This is explicitly concerning for the recipients of angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs), which act, in part, by increasing ACE2 expression [9,10]. The need for this review is highlighted by many clinical reports of neuroinflammation among SARS-CoV-2 patients [11,12,13]. Thus, it is essential to understand the parallel, synergistic, and crosstalk pathways by which ACE2 modulation impacts neurological health. This is crucial knowledge for advancing therapeutic options to circumvent COVID-19. Together, this review unveils possible adverse effects arising from drug-drug interactions in COVID-19 patients with existing co-morbidities, such as hypertension, and explains the mechanisms underlying them. In addition, this review sheds light specifically on the possible impact of blockade of ACE2 in the hypertensive population who are dependent on ARBs/ACEIs.

2. RISK GROUPS FOR COVID-19

Age, diabetes, hypertension and associated co-morbidities are regarded as risk factors for a poor prognosis following SARS-CoV-2 infection [7,14]. The worldwide hypertensive population was estimated to be 1130 million in 2019 [15]. Such a vast hypertensive population is a matter of concern because hypertension is an independent risk factor for type 2 diabetes [16], again the risk factor for COVID-19.

3. ROLE OF ACE2 IN BLOOD PRESSURE REGULATION AND POSSIBLE NEUROINFLAMMATION IN RISK GROUPS

Briefly, ACE2 is a component of the renin-angiotensin system (RAS). The mechanistic pathway of central ACE2 in blood pressure regulation involves the metabolite angiotensin (1-7), a product of angiotensin II hydrolysis by ACE2. Angiotensin (1-7) binds to a G-protein coupled receptor, MAS, and inhibits central norepinephrine release, and has vasodilatory properties. Its absence leads to unchecked sympathetic and diminished parasympathetic activity [5,17]. A recent review collated that local inhibition or global ablation of ACE2 in the brain leads to a decrease in baroreflex sensitivity [17], suggesting a pivotal role of ACE2 in regulating RAS and blood pressure [18].

Furthermore, observations that the overexpression of ACE2 in the brain suppresses angiotensin II-mediated cardiac hypertrophy in animal models [19] suggest that ACE2 has central effects in regulating blood pressure. Hence, it is likely that either inhibition of ACE2 or reduction of ACE2 expression in the brain may worsen blood pressure's central regulation and increase the risks for patients with hypertension and cardiovascular diseases. Thus, using ACE2 blockers in patients with ARBs/ACEIs therapy would have limitations in treating COVID-19 patients with hypertension due to the possible pharmacokinetic antagonism and drug-drug interactions.

The importance of ACE2 in neuroprotection is inferred from two facts. Firstly, the brain possesses its independent RAS with a higher level of angiotensin II than the systemic level. Secondly, ACE2 protects against ischemic brain injury; it protects against reactive oxygen species (ROS)-induced damage by controlling NADPH oxidase/endothelial nitric oxide synthase pathways [20,21]. Further evidence of its protective effect was provided by another study, which reported that ACE2 gene therapy was effective in alleviating hypertension-associated dysautonomia and oxidative stress [22]. Thus, blocking ACE2, as a treatment strategy for COVID-19, increase ROS insult to the brain. Irrespective of its source, ROS can generate a variety of DNA lesions or damage [8].

Mitochondrial DNA (mtDNA) has a higher susceptibility to damage than nucleic DNA due to the absence of histone-like proteins and its proximity to the source of oxidants (the respiratory chain). This inherent susceptibility, combined with a diminished DNA repair capacity, increases the frequency of mutations in mtDNA [23]. Many neurodegenerative conditions are now thought to have a neuroinflammatory component, and such mutations in mtDNA had the potential to induce neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease [24]. While the amyloid hypothesis [25], which relates neurodegeneration in Alzheimer's disease to the buildup of amyloid-beta (Aβ), remains the dominant theory to explain the etiology of this disorder, the onset of neuroinflammation within the condition may be driven by the accumulation of damaged DNA. The accumulation of damaged mtDNA generates mitochondrial ROS, which may activate amyloidogenic enzymes to generate amyloid-beta (Aβ) peptides. These Aβ peptides can hinder ATP production in a free radical-dependent manner[26]. This may, in turn, disrupt mitochondrial transport along the axon [27] and contributes to neurodegeneration of the brain [28]. All the above reports complement the finding that stimulation of the ACE2-Angiotensin (1-7)-Mas axis alleviates cognitive deficits in the experimental rat model of Alzheimer's disease, most probably through the activation of the PI3K/Akt pathway [29]. Thus, blocking ACE2 may trigger neuroinflammation, initiated by ROS and exacerbated by Aβ peptide in these conditions.

ARBs and ACEIs are the most prevalently used among various anti-hypertensive agents and are generally considered safe for COVID-19 patients [30]. The therapeutic effect of ACEIs in individuals with hypertension is mediated partly by ACE2 [5]. Similarly, ARBs/ACEIs upregulate central ACE2 expression and consequently reduce cardiac hypertrophy [19]. However, a key concern is the role of ACE2 as the portal for SARS-CoV-2 entry into cells [31,32]. Therefore, ACE2 receptor blockers, such as chloroquine phosphate, hydroxychloroquine, and DX600, have been proposed as therapies to inhibit the cellular entry of SARS-CoV-2 [3]. Hydroxychloroquine prevents terminal phosphorylation of ACE2 and elevates pH inside lysosomes

and late endosomes to prevent endocytosis of SARS-CoV-2 [3,33]. Thus, these agents block not only ACE2 receptor activation but also impede endocytic pathways and consequent viral replication.

Nevertheless, the administration of these drugs raises other concerns because of the tissue expression of ACE2. In addition to the surface expression of ACE2 in the type II cells of alveoli and enterocytes of the small intestine, it is also found in the endothelial cells of arteries and veins. It is also located in smooth muscle cells of the artery running through the brain, heart, kidney, spleen, liver, small intestine, colon, lymph nodes, thymus, bone marrow, skin, and others [7,20,34]. Its ubiquitous presence highlights its physiological importance and raises concerns about the blockade of the ACE2 receptor, especially in the brain, which shows both neuronal and glial expression of this receptor [17]. ACE2 has been found in different brain compartments, including the cardio-respiratory neurons of the brainstem, motor cortex, and raphe nuclei [17]. The beneficial effect of central ACE2 expression in cardiovascular function has already been discussed [19]. Thus, because of the large number of hypertensive individuals, it is essential to predict the effect of concomitant administration of ACE2 receptor blockers with ARBs/ACEIs and explore the likely consequences in hypertensive COVID-19 patients.

4. ROLE OF ACE2 IN THE METABOLISM OF OTHER PEPTIDES AND THEIR RELATION TO NEUROINFLAMMATION

ACE2 metabolizes several peptides (**Table 1**) (Fig. 1). ACE-2 metabolizes Apelin-13 [17]. Apelin-13 activates pathways such as adenosine monophosphate-activated protein kinase/glycogen synthase kinase 3 beta / nuclear factor erythroid 2-related factor 2 (AMPK/GSK-3β/Nrf2). Activation of this pathway by AR/Gα/PLC/IP3/CaMKK signaling provides neuroprotection by increasing the expression levels of Nrf2-regulated antioxidant enzymes [35]. Apelin-13 has many protective roles in the brain, including reduction of infarct size, improved neurological outcomes, reduced brain edema, inhibition of cell apoptosis, protection from oxidative stress, and neuroinflammation after ischemia-reperfusion following cerebral artery occlusion in rats [35]. Stimulation of the apelin-13 receptor with exogenous apelin 13 has been reported to activate neuroprotective pathways in the brain partly via the adenosine monophosphate-activated protein kinase / thioredoxin-interacting protein /NOD-like receptor pyrin domain-containing 3 protein (AMPK/TXNIP/NLRP3) [36]. In addition, stimulation of the apelin-13 receptor reduces endoplasmic reticulum stress-associated TXNIP/NLRP3 inflammasome activation and attenuates subsequent oxidative stress-induced neuroinflammation/early brain injury [36]. Since ACE2 metabolizes apelin-13, its beneficial effects in these systems may be questionable. However, apelin itself induces the expression of ACE2 to counteract angiotensin II, and, in the apelin knockout mice, the loss of apelin augments the pathological response to angiotensin II [37]. It is noteworthy that inhibition of ACE2 potentiates the hypotensive effect of apelin 13 [38]. All the above studies demonstrate the balancing role of ACE2 on the expression level of apelin. This suggests that ACE2 will ameliorate any serious consequences due to a prolonged hypotensive state induced by apelin.

ACE2 also metabolizes neurotensin [17]. Neurotensin increases glutamate excitotoxicity in both mesencephalic and cortical neurons. Hence, neurotensin can contribute to neurodegenerative conditions such as Alzheimer's and Parkinson's disease [39]. Neurotensin increases the gene expression and release of the proinflammatory cytokine IL-1β, chemokine (C-X-C motif) ligand 8 (CXCL8), chemokine (C-C motif) ligand 2 (CCL2), and CCL5 from human microglia. Neurotensin also increases the proliferation of microglia in the brain. An elevated serum level of neurotensin is correlated with autism spectrum disorders among children [40]. Thus, by regulating the circulating level of neurotensin, ACE2 could suppress neuroinflammation.

ACE2 also has a role in metabolizing kinetensin [17]. Kinetensin shares some sequence homology with the C-terminal end of neurotensin but generally undergoes metabolism two hundred times faster than neurotensin. Kinetensin is rapidly degraded. Therefore, its physiological contributions are limited. However, it is recognized for its role in local histamine release, and it is speculated that kinetensin is an inflammatory mediator that acts in a paracrine manner [41]. Thus, kinetensin metabolism by ACE2 may reduce local inflammation.

ACE2 is also known to metabolize dynorphin [17]. Dynorphin protects dopaminergic neurons in the nigrostriatal pathway through its anti-inflammatory effects. Thus, it may have a protective role in Parkinson's disease [42]. However, excess levels of dynorphin have been linked to glutamate receptor-mediated excitotoxicity. For example, increased prodynorphin gene expression and aberrant processing were shown to be responsible for generating dynorphin derivatives that were toxic to neurons and oligodendroglia [43]. This suggests that ACE2 may reduce neurotoxicity by metabolizing excess dynorphin.

Both [des-Arg9]-bradykinin and [Lys-des-Arg9]-bradykinin are endogenous ligands of bradykinin (B1 and B2) receptors. Both receptor paralogues are present in neurons and glia [44]. ACE2 also metabolizes [des-Arg9]-bradykinin and [Lys-des-Arg9]-bradykinin [17].. In cerebral venular capillaries, [des-Arg9]-bradykinin increases permeability through B2 and B1 bradykinin receptors [45]. In transgenic mice, overexpressing B1 receptors and intravenous administration of [des-Arg9]-bradykinin led to increased hypertensive response and susceptibility for inflammation [46]. B2 receptor was observed to be involved in cell death and brain edema formation following experimental stroke [47]. During a hemorrhagic stroke, the vascular barrier in the brain degenerates, and leakage increases under chronic inflammatory conditions. When the leakage becomes chronic, the extravasation of macromolecules and blood cells triggers edema and inflammation-related disease [48]. The above studies implicate [des-Arg9]-bradykinin in these pathophysiological processes. Since [des-Arg9]-bradykinin is a well-known inflammatory mediator [49], its metabolism by ACE2 produces an anti-inflammatory effect. Similarly, [Lys-des-Arg9]-bradykinin was observed to mediate electrically stimulated- glutamate overflow in rat models of

epilepsy via the B1 bradykinin receptor [44]. Epileptogenesis may be triggered by neuroinflammation, and the persistence of post epileptic neuroinflammation leads to disease progression and neurological co-morbidities [50]. Hence, metabolism of [Lys-des-Arg9]-bradykinin by ACE2 may reduce the risk of epilepsy and neurological co-morbidities. Together, ACE2 likely plays a significant role in suppressing the B1 and B2 receptor-mediated pathological roles of [des-Arg9]-bradykinin and [Lys-des-Arg9]-bradykinin. Thus, monitoring the expression level of these peptides in hypertensive individuals with SARS-CoV-2 infection may identify any potential neuroinflammation arising from drug-drug interactions between ACE2 blockers and ARBs/ACEIs.

Table **1**. ACE2 and their concentration-dependent physiological effects of metabolizing the peptides.

5. CLINICAL RELEVANCE OF ACE2 IN COVID-19 PATIENTS

SARS-CoV-2 invasion has been found to orchestrate neurological manifestations, including encephalitis and many others [11,12,13]. In this regard, a recent study in transgenic animals reported that entry of SARS-CoV-2 through the ACE2 receptor was followed by the downregulation of ACE2 with concurrent cytokine storm [51].

This suggests that further analysis of the intrinsic associations between ACE2 and neuroinflammation is warranted. Furthermore, a clinical study on a diabetic population reported that SARS-CoV-2 invasion induced decreased expression level of ACE2 in blood vessels [52]. This indicates that if patients with SARS-CoV-2 are being treated with ACE2 inhibitors, ACE2 functions may be downregulated by two different mechanisms. Firstly, due to the virus and secondly, due to the ACE2 inhibitors. This may eventually contribute to a cytokine storm and consequent poor prognosis for the patient. Together, an ACE2 blockade will also impact the neuroprotective role of ARBs/ACEIs by altering vascular dynamics [52]. Perhaps, the importance of ACE2 is indicated by a meta-analysis, which concludes that treatment of hypertensive patients with ACEIs/ARBs leads to reduced severity of SARS-CoV-2 infection and mortality [53]. Though the role of angiotensin in neuroinflammation and neurodegeneration has been established [54], further study of ACE2 concerning blood pressure and neuroinflammation cascades is warranted.

The relation between ACE2 blockade and inflammation is also corroborated by a report of ACE2 deficiency-induced muscle weakness and senescence [12]. A decrease in ACE2 is associated with the diminished activity of muscles of respiration, leading to respiratory distress in SARS-CoV-2 patients. In this regard, ACEIs/ARBs have been efficacious in improving muscular activity/performance [12]. Other than skeletal muscle and respiratory muscle weakness [12], SARS-CoV-2 infected patients have many other neurological manifestations like ageusia, anosmia, disorientation, neuropathic pain, seizures, and strokes [55]. These manifestations perhaps suggest a need to observe their relationship with an ACE2 blockade because suppression of ACE2 may be either due to SARS-CoV-2 itself or due to the ACE2 blockers [3,51]. Consistent with our proposals, a blockade of ACE2 is linked with ageusia, a proven adverse effect of ACE2 inhibitors [56]. The mechanism behind anosmia is somewhat complex because ACE2 is not expressed in olfactory neurons. However, it is found in support cells of the olfactory mucosa, Bowman's glands, and on the apical surface of the neuroepithelium cells [57]. The precise mechanism behind anosmia in SARS-CoV-2 cases is still under debate, and it is noteworthy that this manifestation may be reversible within 1-2 weeks. However, there is a report on anosmia two years post-SARS infection [56]. It is hypothesized that viral spike proteins instigate olfactory neurons to release large amounts of IL-6, leading to neuronal damage in the olfactory bulb and subsequent anosmia [56]. This effect may be exacerbated by ACE2 inhibition because an ACE2 blockade may produce IL-6 via angiotensin II-mediated mechanisms [58]. Thus, usage of ACE2 inhibitors induces these effects and exacerbates them by further potentiating any suppression of ACE2 by SARS-CoV-2. This type of interaction may also aggravate neuropathic pain, which is linked to an ACE2 blockade [59]. Similarly, there are reports on the protective effect of ACE2 in seizures, ischemic and hemorrhagic stroke [60] and previously mentioned in this review. All the above factors regarding the role of ACE2 in neurological manifestations in SARS-CoV-2 patients demand further study to elaborate on the mechanism involved with neuroprotection and neuroinflammation.

Fig. (1). (a) Role of ACE-2 in lungs towards SARS-CoV-2 entry and the impact of ACE-2 blockade in brain.

6. ACE2 AND ANGIOTENSIN (1-7)

Obesity has a higher mortality risk from SARS-CoV-2 infection due to the expression of a significantly higher amount of ACE2 by the adipocyte than alveolar epithelial cells in the lung [62]. However, certain evidence speaks in favour of the expression and role of ACE2 and angiotensin (1-7) in obesity[63]. It is reported that ACE2 and angiotensin (1-7) reduce inflammation of epicardial adipose tissue and activation of macrophages into a proinflammatory phenotype. This reduces cardiac steatosis, lipotoxicity and prevents heart failure [63]. While considering the role of ACE2 in obesity, it is perhaps better to consider the coexistence of hypertension among the patients because the obese population presents a 3.5 fold increased probability of developing hypertension, and 60 percent of hypertensive people are overweight [64]. The correlation between obesity and hypertension suggests ACE2 as a double-edged blade. One way, its upregulation is considered the reason behind increased mortality in SARS-CoV-2 patients [62] and its absence will worsen the cardiovascular complications in obesity [63]. This actually underscores the importance of ACE2, especially in obese hypertensive population. On a similar note, the benefits of ACE2 and angiotensin (1-7) are evident from the recommendation that ACE2-angiotensin (1-7)-Mas receptor axis in the lung prevents bradykinin-induced inflammatory process and has an anti-thrombotic effect. Further, suppression of ACE2-angiotensin (1-7)-Mas receptor axis in the lung by the SARS-CoV-2 leads to the devastating impact of angiotensin II, which include alveolar

wall thickening, edema, infiltrates of inflammatory cells, bleeding [65]. ACE2 and angiotensin (1-7) have a positive association in modulating neurologic benefits and, thus, their augmentation by therapeutics could affect COVID-19 prognosis. Furthermore, the impairment of ACE2 and angiotensin (1-7) in the inflamed adipose tissue in obese individuals with COVID-19 infection would worsen the neural profile. This once again proves the importance of ACE2 in the context of SARS-CoV-2 disease.

7. DISCUSSION

The literature collated above provides a strong background on the possible impact of ACE2 blockade in ARBs/ACEIs dependent patients.

ARBs and ACEIs are the first-line drugs for hypertension [66]. ARBs are well known to prevent oxidative stress induced by angiotensin II in hypertensive patients and prevent many risk factors known to be important for neurodegenerative diseases such as Alzheimer's disease [67]. Both ARBs and ACEIs exert their therapeutic effects partly by upregulating ACE2 [7,9,10]. This warrants contemplation on the usage of ACE2 blockers to prevent SARS-CoV-2 invasion in hypertensive individuals already on ARBs/ACEIs therapy. The finding highlights the consequence of an ACE2 blockade that microangiopathy is responsible for diabetic neuropathy, and ACEI, such as quinapril, significantly improved peripheral neuropathy [68]. These findings implicate ACE2 in both central [24] and peripheral neuropathy [68]. This theory is strengthened by the role of ACE2 in suppressing neurotoxicity by metabolizing an excess amount of angiotensin-II, apelin-13, neurotensin, kinetensin, dynorphin, prodynorphin, [des-Arg9]-bradykinin, and [Lys-des-Arg9]-bradykinin. ACE2 blockers may suppress the efficiency of ARBs/ACEIs, leading to an increase in blood pressure, cardiovascular mortality. In addition, they may increase the chance of neuroinflammation as a result of non-specific pharmacological mechanisms. This could exacerbate the severity and associated mortality of SARS-CoV-2 infections in hypertensive individuals.

Neurotoxicity due to hydroxychloroquine can occur under various circumstances related to dose, length of administration, specific drug interactions, and pre-existing neuropathies [69]. Added to this, infection with SARS-CoV itself can induce neuroinflammation [70]. Dormant neuroinflammatory conditions may also aggravate the chance of full-fledged neuroinflammation [66]. Additionally, reports of central venous thrombosis have occurred in cases where previously healthy young patients have been treated with hydroxychloroquine and azithromycin. However, whether this embolism was a result of drug treatment or infection, is not clear [13]. The mechanism by which cerebral venous thrombosis is linked with neuroinflammation in both normal and COVID-19 conditions remains elusive. An urgent focus on this outcome is warranted, as central venous thrombosis may be either lethal or permanent disability [71].

It is noteworthy that the implications of an ACE2 blockade may have either a SARS-CoV-2 origin or ACE2 inhibitor origin. Since ACE2 inhibitors can potentiate SARS-CoV-2 mediated ACE2 suppression and counteract the beneficial effect of ACEIs/ARBs, the co-administration of ACEIs/ARBs with ACE2 inhibitors deserves reconsideration with regards to neuronal health. However, the incidence of neuroinflammation in hypertensive COVID-19 patients will likely depend on the dose and duration of treatments and on the patient's individual susceptibility. This suggests the importance of monitoring neuronal function, especially in children and older adults, during therapy with ACE2 blockers and ARBs/ACEIs. In addition to checking for the possibility of neuroinflammation following ACE2 blockade, further research is required to pinpoint the mechanisms underlying it. The possible intermediates whose ACE2 dependent metabolism may prevent neuroinflammation have been discussed above.

Hence, further research is required to establish the links between SARS-CoV-2, pharmacological treatments, and neuroinflammation so that any necessary therapeutic measures can be adopted to prevent neuroinflammation.

8. AUTHORS INSIGHT ON THE TOPIC

This review considers the dichotomous role of the ACE2 receptor. One way, it is evident that an increase in the ACE2 receptor in lungs following ARBs/ACEIs treatment will exacerbate SARS-CoV-2 infection, another way, a meta-analysis opposes the possibility. Instead, claims the beneficial effect of ARBs/ACEIs induced upregulation of ACE2 in SARS-CoV-2 patients. Though obesity study associates ACE2 expression with higher mortality risk in SARS-CoV-2 patients, an lack of ACE2 or angiotensin (1-7) has exacerbated the inflammatory condition in obese people and increased the chances of cardiac death failure. As suppression of ACE2-angiotensin (1-7)-Mas receptor axis by SARS-CoV-2 led to severe pulmonary complications, the authors believe that ACE2 inhibition can inhibit SARS-CoV-2 invasion will produce potential neuroinflammation, especially in patients with pre-existing or dormant neuroinflammation.

9. CONCLUSION

The clinical findings suggest that the beneficial role of ACE2 may be impeded by both SARS-CoV-2 and ACE2 inhibitors, leading to neurological manifestations. As ACE2 metabolizes peptides responsible for excitotoxicity in neurons and restores their normal concentration, the ACE2 blockade may attenuate the beneficial effects of ARBs and ACEIs in hypertensive individuals. In addition, the ACE2 blockade-induced unregulated activity of various peptides, resulting from non-specific pharmacological interactions between ARBs/ACEIs and ACE2 inhibitors, may precipitate both central and peripheral neuroinflammation among COVID-19 patients. Hence, monitoring the expression level of these peptides in COVID-19 patients with pre-existing hypertension may be helpful to predict any chances of neuroinflammation and adopt appropriate treatment measures.

LIST OF ABBREVIATIONS

ACE2 = Angiotensin converting enzyme 2

ACEIs = Angiotensin converting enzyme inhibitors

ARBs = Angiotensin receptor blockers

BBB = Blood brain barrier

COVID-19 = Corona virus disease of 2019

DNA = Deoxyribonucleic acid

mtDNA = Mitochondrial DNA

NMDA = N-methyl-d-aspartate

SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Table **1**. ACE2 and their concentration-dependent physiological effects of metabolizing the peptides

Peptides	**Pathological Role**	**Reference**
Angiotensin-II	Hypertension, dysautonomia, oxidative stress, mtDNA damage etc.	[7,30]
Apelin-13	Vasodepressor, hypotensive effect	[37]
Neurotensin	Glutamate excitotoxicity, neuroinflammatory conditions	[41]
Kinetensin	Inflammatory mediator	[43]
Dynorphin and prodynorphin	Glutamate excitotoxicity, neuronal and glial toxicity	[45]
[des-Arg9]-bradykinin	Inflammatory mediator, inflammation of neuron and glia, brain cell death and edema	[47,48,49,51]
[Lys-des-Arg9]-bradykinin	Glutamate excitotoxicity, epileptogenesis and neuroinflammation, neurological co-morbidities	[47,52]

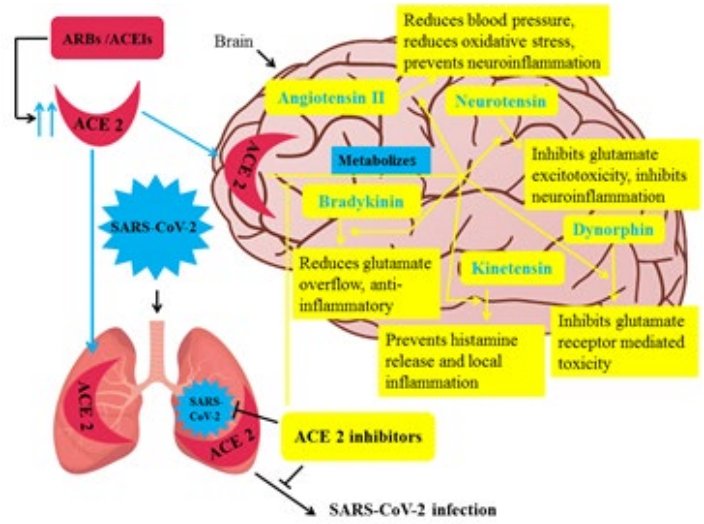

Fig. (1). Role of ACE-2 in lungs towards SARS-CoV-2 entry and the impact of ACE-2 blockade in brain.

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