Mechanical dependency of the SARS-CoV-2 virus and the renin-angiotensin-aldosterone (RAAS) axis: a possible new threat

Rohit Sen¹ · Devashish Sengupta² · Avinaba Mukherjee¹

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Abstract

Pathogens in our environment can act as agents capable of inflicting severe human diseases. Among them, the SARS-CoV-2 virus has recently plagued the globe and paralyzed the functioning of ordinary human life. The virus enters the cell through the angiotensin-converting enzyme-2 (ACE-2) receptor, an integral part of the renin-angiotensin system (RAAS). Reports on hypertension and its relation to the modulation of the RAAS are generating interest in the scientific community. This short review focuses on the SARS-CoV-2 infection's direct and indirect effects on our body through modulation of the RAAS axis. A patient having severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection, which causes COVID-19 relates to hypertension as a pre-existing disease or develops it in a post-COVID scenario. Several studies on how SARS-CoV-2 modulates the RAAS axis indicate that it alters our body's physiological balance. This review seeks to establish a hypothesis on the mechanical dependency of SARS-CoV-2 and RAAS modulation in the human body. This study intends to impart ideas on drug development and designing by targeting the modulation of the RAAS axis to inactivate the pathogenicity of the SARS-CoV-2 virus. A systematic hypothesis can severely attenuate the pathogenicity of the dreadful viruses of the future.

Keywords SARS-CoV-2 · Environmental pathogen · ACE2 receptor · RAAS system · Hypertension

Introduction

The outbreak of COVID-19 due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has affected millions of people globally, wherein about 3.5 million died due to this outbreak (Dyer 2021; Woolf et al. 2021). However, recent data have suggested that the actual global mortality due to COVID infection is almost 6.9 million (Dyer 2021).

Pathogens like SARS-CoV-2 lead to fatal outcomes, especially in immunocompromised patients infected with the virus (Belsky et al. 2021). Differences in mortality rates among different age groups of the population can be linked with the differential status of the endocrine system, behavioral system, and physiological conditions related to the age groups of the infected human population (Undurraga et al. 2021). The pathogenicity of the coronavirus is attributed to the high affinity of the spike protein that binds with the angiotensin-converting enzyme (ACE)-2 receptors, particularly in the lungs. It is known that ACE2 receptors act as an integral part of an axis termed as the renin-angiotensin-aldosterone system (RAAS) (Lavoie and Sigmund 2003; Tikellis and Thomas 2012). There is, therefore, a possibility of modulation of such an essential endocrine axis after COVID infection. Several studies have been made on the impact of COVID on the RAAS axis. However, the current data are scattered in a discrete pattern. In this review, we attempt to summarize the effects of SARS-CoV-2 on the RAAS axis. Also, we have linked the impact of SARS-CoV-2 on RAAS-mediated crosstalk signaling processes such as hypertension and behavioral alteration.

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✉ Avinaba Mukherjee
mukherjeeavinaba@gmail.com

Rohit Sen
robikolom1996@gmail.com

Devashish Sengupta
devashish.sengupta@alumni.sydney.edu.au

¹ Department of Zoology, Charuchandra College, University of Calcutta, 22, Lake Road, Kolkata 700029, India

² Department of Chemistry, Assam University, Silchar, Assam 788 011, India

Effect of SARS-CoV-2 on angiotensin

The RAAS system has a crucial role in controlling the retention of salts and water in the circulatory system via renal reabsorption, thus regulating blood pressure (Vaduganathan et al. 2020). Angiotensin, specifically Ang II, is the main contributor to the RAAS system by stimulating aldosterone secretion, the main end product of the glomerulosa layer, in the adrenal cortex. Membrane-bound aminopeptidase ACE2 is a regulatory enzyme that cleaves the active form of both angiotensin I and angiotensin II into angiotensin 1–9 and angiotensin 1–7, respectively (Kuba et al. 2010; Strawn et al. 1999; Ye et al. 2006). ACE2 maintains the physiological equilibrium between the vasoconstrictor effect of angiotensin II and thus of angiotensin 1–7, which lowers blood pressure by dilating the blood vessels (Fig. 1) (Burrell et al. 2004). However, its infection by SARS-CoV-2 leads to the disruption of the homeostatic environment devised by RAAS. Measuring blood levels of ACE2 after prospective validation is now known to provide a risk-stratification opportunity, leading to the identification of individuals who are at greater risk of infection or are susceptible to experiencing severe medical complications. An opportunistic approach to protect against the SARS-CoV-2 disease may be possible by targeting the ACE2 system. For an individual patient, this may aid in monitoring responses to preventive measures and treatment interventions. Thus, focusing on the potential therapeutic strategy enabled by targeting ACE2 is especially important.

Autopsies of deceased COVID-19 patients show a remarkable decrease in ACE2 expression (Oudit et al. 2009; Chaudhry et al. 2020) along with severe lung injuries (He et al. 2006), due to inhibition of SARS-CoV-2. Further investigations show a correlation between elevated plasma angiotensin II levels and lung injury along with viral load in severely infected patients (Liu et al. 2020; Miesbach 2020), indicating that ACE2 downregulation promotes angiotensin II. The binding of angiotensin II with AT1 receptors can lead to enhanced inflammation, vasoconstrictors, and thrombosis. On

the other hand, angiotensin III is also called as Ang-(2-8). Aminopeptidase A (APA) cleaves the Asp1-Arg2 bond in Ang II and converts it into Ang III. The major function of Ang III is to regulate hypertension and vasopressin release (Reaux et al. 2001).

AT2R is another important factor in RAAS regulation as both angiotensin II and angiotensin III are modulated after SARS-CoV-2 infection. Though AT2R has a significant role in the vasodilation of vascular epithelium AT2R, it lacks any impact in RAAS regulation while Na⁺ excretion through the kidneys increases (Summers et al. 2015). Angiotensin III might positively affect Na⁺ reabsorption indirectly by interacting with AT2R in the zona pellucida of the adrenals, but the concomitance of the vasodepressor is seen when synthetic {beta-Pro (7)} angiotensin III is introduced (Del Borgo et al. 2015). It was earlier reported, due to virus infection, that ACE2 downregulation creates local imbalance between the RAS and ACE2/angiotensin-(1–7)/MAS axis. This might directly lead to severe organ injury. Therefore, the balance between angiotensin I and II, and 1–7 and 1–9, rather than each one alone, may be the main determinant of dysfunctions related to the RAAS (Ni W et al. 2020). As a whole, SARS-CoV-2infection-induced modulation in angiotensin and its related receptor expression leads to several altered physiological conditions in the human body.

Possible partial effect of SARS-CoV-2 on aldosterone

SARS-CoV-2 infection upregulates angiotensin II after binding with the ACE2 receptor (Oudit et al. 2009; Chaudhry et al. 2020) as discussed earlier. On the other hand, angiotensin II upregulates aldosterone secretion (Patel et al. 2017). Therefore, after SARS-CoV-2 infection, there might be a possibility for the elevation of the aldosterone level. However, the reports supporting this are few, but some recent workers have found a positive correlation between upregulated aldosterone levels in COVID-19 patients' bodies (Villard et al. 2020).

Fig. 1 Possible effect of RAAS on blood pressure regulation. Here, ACE2 means angiotensin-converting enzyme 2, AT1R means angiotensin type 1 receptor and AT2R means angiotensin type 2 receptor, ANKY C1 means ankyrin C1 protein, CK1 means casein kinase 1, and ENaC means epithelial sodium channel receptor

Mineralocorticoids provoke the epithelial sodium channel (ENaC), also called amiloride-sensitive sodium channel, a hetero-trimeric ion channel selectively permeable to sodium ion targeting in the principal cell apical surface (Noreng et al. 2018). Aldosterone facilitates ENaC function through mediator protein families of casein kinase (CK), ankyrin G (Klemens et al. 2017), and even circadian rhythm controlling period 1 protein (Gumz et al. 2009). Casein kinase 1 delta/epsilon, a subtype of CK protein, though the mechanism is still unclear, triggers ENaC- α expression (Yan et al. 2007), i.e., it may act upon the transcriptional level of this protein expression. In several studies, CK1 DELTA/EPSILON blockage checks ENaC mRNA expression by restricting PER-1 nuclear entry (Richards et al. 2012). Therefore, a SARS-CoV-2-mediated disruption of the RAAS system not only affects the respiratory and cardiovascular systems but also might trigger the regulation of the circadian cycle. This behavioral alteration might be taken into consideration for COVID-19 patients due to elevated aldosterone.

Possible partial effect of SARS-CoV-2 on NO activity and hypertension

Nitric oxide (NO) is a potent vasodilator; it inhibits the vasoconstriction effects on blood vessels of angiotensin II (Richards et al. 2012). NO not only leads to the reduction of blood pressure by inhibiting the AT1R in the vascular epithelium (Savoia et al. 2020) but also may drive angiotensin II and elevates the interaction of angiotensin II-AT2R. It facilitates the degree of lowering of blood pressure. If administered at the early stages of the infection, NO might play its role in restricting the virus binding to the AT1R in the lungs by hindering AT1R endocytosis of SARS-CoV-2 (Fig. 2).

Modulation of RAAS in other pathological conditions linked with SARS-CoV-2 infection

RAAS is modulated not only in COVID-19 patients but also in several pathological conditions like obesity, diabetes, inflammations, renal disorders, and others, which might be linked with accentuating the effects of SARS-CoV-2 infection and creating comorbidities and asymptomatic disease in the human population. Obesity is yet another critical factor for disrupting the RAAS axis and elevating the renin (Kalil and Haynes 2012) and aldosterone secretion from the adrenal gland (Peminda et al. 2017; Yang et al. 2021). An adipokine named leptin upregulates renin via sympathetic activation through the CNS (brain stem and hypothalamus) (Peminda et al. 2017; Hall et al. 2010). Along with renin, angiotensin II activity is enhanced either by inhibiting ACE2 (Patel et al.

2016; Soler et al. 2013; Kawabe et al. 2019) or facilitating the conversion of angiotensin I to angiotensin II by cathepsins in adipose tissue (Schütten et al. 2017). This deregulated renin/angiotensin/aldosterone axis that pre-exists in obese individuals may aggravate COVID-19. Meta-analytic data shows that the susceptibility to infection of COVID-19 increases a few folds in obese individuals than in non-obese individuals, but also obesity aggravates the severity of the condition (Yang et al. 2021; Hall et al. 2015; Zhang et al. 2021) along with it becoming a strong reason for comorbidities.

On the other hand, obesity is strongly associated as a critical feature of diabetes in which high glucose levels induce the release of renin, as reported by Toma et al. (2008). Hyperactivation of the RAAS axis can therefore be observed in diabetic patients (Ribeiro-Oliveira Jr et al. 2008). Hyperactivation of the RAAS axis could consequently help in the invasion of SARS-CoV-2. This observation is supported by some recent data, which shows that diabetic patients are more prone to SARS-CoV-2 infectivity and mortality (Feldman et al. 2020). Besides this, in diabetic patients, monocyte and macrophage activation occur, which creates an elevation of proinflammatory cytokines and chemokines like TNF α , IL6, IL8, and others (Kurihara et al. 2012). The heightened proinflammatory cytokines and chemokines create inflammation in the body that might play a vital role in SARS-CoV-2 infection, especially in the generation of asymptomatic disease (Xie et al. 2021).

Among the renal abnormalities associated with COVID-19 reports include proteinuria, hematuria, and acute kidney injury. SARS-CoV-2 can infect podocytes, and tubular epithelial cells, contributing to the aforementioned renal abnormalities. The renal abnormalities associated with COVID-19 are related to the rise in the complex multifactorial pathophysiology involving the following: (i) a local disruption in RAAS homeostasis, (ii) a direct cytopathic effect of the virus, and a systemic inflammatory response to infection (Martinez-Rojas et al. 2020). ACE2 supports renal integrity and function through the enzymatic production of angiotensin 1–7 (Ang1–7). Widely expressed ACE2 in proximal epithelial cells, smooth muscle cells, vascular endothelial cells, and podocytes acts as an anti-inflammatory, antifibrotic, vasodilatory, and diuretic/natriuretic agent via activation of the Mas receptor axis. Upon disruption of these activities in the kidneys by ACE2, potential threats of renal damage leading to a high incidence of acute kidney injury (AKI) among SARS-CoV-2 patients are reported (Armaly et al. 2021). The exogenous administration of Ang (1–7) is considered an appealing therapeutic option, given the benefits of ACE2/Ang1–7, including attenuation of inflammation, vasodilation, diuresis, apoptosis, natriuresis, oxidative stress, coagulation, and cell proliferation, as well as the high incidence of AKI in these ACE2-depleted disorders (Martinez-Rojas et al. 2020; Armaly et al. 2021).

Fig. 2 Possible role of SARS-CoV-2 infection and alteration in the RAAS axis

Drugs that are capable of addressing the alteration in the RAAS axis

Many drugs have been administered to block the RAAS axis. Some of these drugs are aldosterone receptor antagonist, angiotensin-converting enzyme inhibitors (ACEi), sodium channel blocker, and potassium-sparing channel blocker, among others (Table 1). However, due to the COVID outbreak, the main drug target area has also been modulated so that the pathogen can thrive in the human body and serve its detrimental effect by altering the RAAS axis.

Possible drug target area

Prompted by the fact that elderly patients with cardiovascular comorbidities have been gravely affected by the severe forms of SARS-CoV-2, interpretations based on retrospective observational studies about the influence of chronic treatment with drugs that are blockers of RAAS are ongoing. However, these retrospective interpretations should be published with caution and only evidence-based data on the impact of RAAS-interfering medications in patients and the general population should be published. Under *in vivo* conditions, reports on 15 classes of drugs in increasing ACE2 levels and a reanalysis of clinical data available from literature from a meta-analysis of 9 studies have shown that an increased risk of mortality is not connected with the usage of ACEIs/ARBs (Akhtar et al. 2020; Kai and Kai 2020; Yehualashet and Belachew 2020). Though research on some animal sources implies enhancing ACE2 expression or activity by drugs against hypertension, data

obtained on humans show a contradiction of increased expression of the transmembrane ACE2 protein in the lung brought about by anti-hypertension medications. Cardiovascular conditions can influence the expression of ACE2 in humans, which is independent of RAAS-blockade strategies of treatment (Kai and Kai 2020; Gheblawi et al. 2020; Yehualashet and Belachew 2020). A change in the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) is not required to address the management of elevated blood pressure in the treatment of COVID-19 infection (Gressens et al. 2021). Though it is controversial whether regular usage of these drugs affects ACE2 expression or not, studies showed chronic hypertensive patients tend to have severe symptoms, and hypertension remained one of the main factors for comorbidity (Clark et al. 2021). There is still no evidence for the involvement of elevated ACE2 in plasma levels before infection due to the daily dosage of ARBs and AREs (Ni et al. 2020). Studies show varied responses in patients to ACE2-modulating drugs. Thus, the therapeutic application of such drugs also varied; most of them prescribed persistence of medication. Alternative medication had been devised in cases where AREIs and ARBs show adverse effects (Jarari et al. 2016). Detailed studies on the impact of antihypertensive drugs on ACE2 needed to be done, shedding light on the mechanisms and critical details affecting hypertension.

Since more severe hyper-mutative variants of the COVID-19 virus are being identified, alternative approaches exploring the modulation of the specific downstream pathophysiologic effects caused by a virus that leads to morbidity and mortality are being researched (Gressens et al. 2021). Opportunities to understand the various aspects of RAAS inhibitors to alleviate

Table 1 List of RAAS inhibitors, their structures, and mechanism of action

Name of Inhibitors that act as drug	Structure of the drug	Mechanism of Action
A. RAAS blocker/inhibitor		
i. Direct Renin inhibitor (e.g; Aliskiren)		Competitive renin inhibitor which binds to the active site of the enzyme (Wood 2003)
	<p>Molecular formula: C₃₀H₅₃N₃O₆</p>	
ii. Angiotensin-2 receptor blocker (ARB)		It blocks the Aldosterone receptor and modulates its activities.
a) Valsartan	<p>Molecular Formula: C₂₄H₂₉N₅O₃</p>	Modulates the mRNA expression of ACE and AT1R (Li et al. 2016)
b) Irbesartan	<p>Molecular Formula: C₂₅H₂₈N₆O</p>	It selectively and competitively blocks the binding of angiotensin II to the angiotensin I receptor. Angiotensin II stimulates aldosterone synthesis and secretion by the adrenal cortex, which decreases the excretion of sodium and increases the excretion of potassium. Angiotensin II also acts as a vasoconstrictor in vascular smooth muscle (Hartner et al. 2014).
c) Losartan		Losartan and its active metabolite

	<p>Molecular Formula: C₂₂H₂₃ClN₆O</p>	<p>selectively and competitively block the binding of angiotensin II to the angiotensin I (AT1) receptor. This blocks the vasoconstrictive and aldosterone-secreting actions of angiotensin II, leading to a decrease in blood pressure. Angiotensin II, formed from angiotensin I by angiotensin-converting enzyme (ACE), stimulates the adrenal cortex to synthesize and secrete aldosterone, which decreases the excretion of sodium and increases the excretion of potassium. Angiotensin II also acts as a vasoconstrictor in vascular smooth muscle (Timmermans et al. 1995).</p>
iii. Angiotensin Converting Enzyme Inhibitor (ACEi)		Blocks of activation of Angiotensin-converting enzyme and ANG 1-7 Mas receptor.
a) Benazepril		It competitively binds to and inhibits ACE, thereby blocking the conversion of angiotensin I to angiotensin II. This prevents the potent vasoconstrictive actions of angiotensin II

	<p>Molecular Formula: C₂₄H₂₈N₂O₅</p>	<p>resulting in vasodilation. Benazeprilat also decreases angiotensin II-induced aldosterone secretion by the adrenal cortex, which leads to an increase in sodium excretion and subsequently increases water outflow (Liu et al 2011).</p>
b) Lisinopril (dihydrate)	<p>Molecular Formula: C₂₁H₃₅N₃O₇</p>	<p>Competitively inhibits ACE, which results in a decrease in the production of the potent vasoconstrictor angiotensin II and, so, diminished vasopressor activity. In addition, angiotensin II-stimulated aldosterone secretion by the adrenal cortex is decreased, which results in a decrease in sodium and water retention and an increase in serum potassium (Iyer et al. 1998).</p>
c) Enalapril		<p>It competitively binds to and inhibits ACE, thereby blocking the conversion of angiotensin I to angiotensin II. This prevents the potent vasoconstrictive actions of angiotensin II and</p>

	<p>Molecular Formula:$C_{20}H_{28}N_2O_5$</p>	<p>results in vasodilation. Enalapril also decreases angiotensin II-induced aldosterone secretion by the adrenal cortex, which leads to an increase in sodium excretion and subsequently increases water outflow (Hair et al. 2007).</p>
B Epithelial Na^+ Channel (ENaC) Blocker.		
a) Amiloride	<p>Molecular Formula:$C_6H_8ClN_7O$</p>	<p>Directly blocks Epithelial sodium channels (Kleyman 1988, Vandenbeuch 2020).</p>
C. K^+ sparring diuretics		
a) Spironolactone	<p>Molecular Formula:$C_{24}H_{32}O_4S$</p>	<p>Competitively blocks the aldosterone receptors (Layton 2017).</p>

indirect viral-induced lung and other organ injuries are getting attention (Ingraham et al. 2020). Patients with cardiovascular comorbidities are often administered RAAS blockers. The degree of ACE2 expression in different age groups combating severe infection of the virus and mortality is being hinted at being directly related to the incidence and severity of COVID-19 virulence. The benefits or risks of pharmacologic modification of the RAAS-SCoV-axis by drugs that are possible angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are still not very clear (Gressens et al. 2021). The possibility that these drugs may facilitate viral cell entry has fueled controversies since the expression of ACE2 may be increased by RAAS blockers, yet by degrading angiotensin II into angiotensin, ACE2 functions as a counter-regulator of the RAAS (Gressens et al. 2021). While the former has led to concerns that such modulations may aggravate and worsen the condition of the patients, the latter may mediate beneficial effects in COVID-19. The contemporary experimental models through relevant preclinical approaches favor a protective outcome of RAAS-CoV-axis inhibition on both lung injury and survival. But there are limitations in clinical data related to the role of RAAS modulation in the setting of SARS-CoV-2. A clinical equipoise regarding the efficacy of RAAS-based interventions and the imminent need for a multisite randomized controlled clinical trial to evaluate the inhibition of the RAAS-SARS-CoV-2 axis on acute lung injury in COVID-19 has been proposed (Ingraham et al. 2020). Based on viral microbiology, the target of the various proposed interventions for SARS-CoV-2 and the inhibition of viral cellular injury have been proposed (Ingraham et al. 2020).

There is evidence that there may be a relation between ACE2 and the differences in incidence and severity of COVID-19 infection (Kaseb et al. 2021). The prevalence and severity of COVID-19 among the vulnerable groups of patients having age-related comorbidities with established high levels of ACE2 expression establish its candidacy as a potential therapeutic target. Evidence supports the idea that differences in the incidence and severity of COVID-19 infection may be related to ACE2 (Kaseb et al. 2021). The prevalence and severity of SARS-CoV-2 among age- or gender-, or ethnicity-related comorbidity, with established high levels of ACE2 expression, strongly support this inference. The burden of COVID-19 infection in these vulnerable groups added to the impact of the potential therapeutic and preventive measures as a result of adopting ACE2-driven anti-viral strategies; the expedition of a global approach to control the severe infection and mortality of the COVID-19 pandemic may be possible (Kaseb et al. 2021). Though in-depth clinical and mechanistic investigations are still ongoing, literature is indicative of the safety in the usage of ACEIs/ARBs, though, in severe COVID-19 patients, there may be an increased risk of renal injury (Akhtar et al. 2020).

Internalization of ACE2 by SARS-CoV-2 upon entry into the target cell likely reduces cell-surface ACE2 levels, thus translating into (i) the downregulation of Ang-(1–7), (ii) causing unopposed Ang II accumulation, and (iii) RAAS activation promotion (Kaseb et al. 2021). ACE inhibitors and Ang II-receptor blockers as RAAS inhibitors serve as potential therapeutic strategies to prevent SARS-CoV-2 infection. Other options include modifying ACE2 levels or activity in the target cells. As such, the therapeutic approaches for achieving the mentioned options are achievable by blocking spike-protein priming by employing TMPRSS2 inhibitors, slowing the viral entry into target cells by using soluble recombinant ACE2 to competitively bind with the COVID-19 virus serving as a virus trap and inactivator, and developing a vaccine targeting the spike protein of SARS-CoV-2 (Kaseb et al. 2021; Ferrario et al. 2005; Akhtar et al. 2020).

ACE2 is a membrane-bound aminopeptidase. The composition of ACE2 is attributed to a carboxymonopeptidase that prefers hydrolysis between proline and carboxy-terminal hydrophobic residues that is found both as a membrane-associated and as a secreted enzyme in cardiovascular, neuronal, and reproductive organs (Ferrario et al. 2005). Angiotensin I and angiotensin II are cleaved into the angiotensin-(1–9) and angiotensin-(1–7) peptides by ACE2 (Mourad and Levy 2020). ACE2 is overexpressed in heart failure, arterial hypertension, and diabetes mellitus. The existence of a cardiovascular-protective ACE2–angiotensin-(1–7)–Mas receptor axis is supported in several studies (Ferrario et al. 2005). Activation of ACE2 is known to modulate the host and support its replication. Investigations about the role of ACE2 in activating the immune signals on SARS-CoV-2 attachments have prompted the construction of the host regulatory network upon the viral attachment to the ACE2 receptor, specifically in the lungs (Lite et al. 2021). The gene-expression profile of the human lung was integrated with the host regulatory network to investigate the altered host signaling mechanism prevalent in the SARS-CoV-2 viral infection. The immune modulation in the constructed network, comprising 133 host proteins with 298 interactions that directly or indirectly connect to the ACE2 receptor, was also determined by functionally enriching the network. Results show that upon infection by SARS-CoV-2, the host lungs differentially regulated 29 proteins out of the 133 host proteins. The generation of a new network of the altered proteins by connecting with multiple proteins was observed to modulate kinase, cytokine, and carboxypeptidase activity. This modulation leads to changes in the host immune system, signal transduction mechanism, and cell cycle. Secondary health complications were apparent from an investigation indicating similar signaling events in the kidneys, pancreas, small intestine, testes, placenta, and adrenal glands (Lite et al. 2021). The interconnected protein hubs are assumed to be activated when the SARS-CoV-2 virus binds with the ACE2 receptor. The direct mediators of these protein hubs were AGT

(Angiotensinogen), LAMAS (Laminin Subunit Alpha 1), NTS (Neurotensin), GHRL Ghrelin, and (ObestatinPrepropeptide) as revealed by the Interactome data. The association of a regulatory network with various biological pathways responsible for the disease, immune system, DNA repair, cell cycle, autophagy, programmed cell death, transcription, and signal transduction was revealed by the Reactome database (Lite et al. 2021). The presence of ACE2-inducible immune factors across different tissue types was found to be very profound in the lungs compared to other tissues, thus making it more sensitive. The overactive immune response leading to respiratory illness could be an underlying molecular factor (Lite et al. 2021).

ACE2 modulator drugs such as angiotensin-converting enzyme inhibitor (ACEi) though having a suppressing effect on ACE2-induced hypertension and being reported to decrease mortality (Chu et al. 2021) but less likely to be used in patients with a prior chronic medical condition (like hypertension, diabetes mellitus, cardiovascular disease) may show unlike effects (Fang et al. 2020). In contrast to Na^+ absorption, K^+ secretion occurs through the cells of the epithelial lining of the renal tubule, but in COVID-19, uncontrolled K^+ secretion may induce a hypokalemic condition in infected individuals (Moreno-P et al. 2020) leading to the requirement of ventilation support required by severely infected patients. But a high K^+ concentration in the blood has an inhibitory role in the RAAS system (Poulsen and Fenton 2019); thus, K^+ -sparing drugs such as spironolactone is prescribed in few cases as an alternative way of combating SARS-CoV-2 by bypassing the adverse effects of ARBs and ACE (Cadegiani et al. 2020).

In another article (Gumashta and Gumashta 2020), it is suggested that AT2R agonists might be a way to reduce the severity of the patients. Thus, it is well implicated that the ANG III/AT2R might be a new axis to be considered in drug designing.

The aforementioned K^+ -sparing diuretics do not only increase K^+ reabsorption (Cadegiani et al. 2020) but may also increase Na^+ secretion by blocking the ENaCs (Fang et al. 2020). Amiloride, a potent potassium-sparing diuretic, has multivariate potential as it not only suppresses the ENaC activity (Bhagatwala et al. 2014) but also has a direct effect in reducing blood pressure, cardiovascular risks, and often edema observed during COVID infection (Hinrichs et al. 2018). Since aldosterone blockers might hamper the activity of ACE2 (Fang et al. 2020), ENaC-blocking drugs might be another bypass to adverse coronary effects. Research on SARS-CoV-2 survivors with chronic hypertension and without any hypertension is yet to be done, though ACE2 modulation may affect them in the future.

Despite such a lack of knowledge of the risk of recurrence of Covid-19, long-term effects of medication and weakened immunity may trigger the infection again. However, reinfection of SARS-CoV-2 is still unknown. Also, the possibility of

reinfection with SARS-CoV-2 is poorly understood. However, some recent works have found two distinct significant genetic variants of SARS-CoV-2 infection in the same individual and were reported to be a case of reinfection of SARS-CoV-2 (Tillett et al. 2020). But as such, the possibility of reinfection with SARS-CoV-2 is not well understood. Apart from vaccines, alternative medicines are available, and new medication with low side effects and preventive organ effects in this extraordinary situation may find a possible way out.

Conclusion

This review highlights how SARS-CoV-2 infection in synergy with the RAAS axis can inflict the modulation of the RAAS axis. Furthermore, this complex loop interdependence between RAAS and SARS-CoV-2 gets more complicated as apparent in several pathophysiological conditions like diabetes; RAAS axis modulated by immunosuppressive conditions may accelerate the infectivity of SARS-CoV-2 because these diseases are known to raise the comorbidity. Overall, the present review implies how COVID patients bear the alteration in their RAAS axis and, therefore, changes in the physiological and behavioral aspects are brought about. Chronic hypertensive individuals can be more susceptible to recurrence of the disease than the normal ones (Clark et al. 2021). Reinfection might be another problem that may arise in the future with a different and possibly more lethal strain of the SARS-CoV-2 virus.

The development of new target-specific drugs against hypertension, i.e., less dependent on ACE2, is vital. Other than that, modifying ACE2 levels or activity in the target cells is highly solicited. Though this review ceases to show any reports of hypertension in COVID-19 survivors, active involvement of RAAS might be a possibility in triggering hypertension in high-risk groups of the population. Infected patients may bear the alteration in blood pressure and hypertension state through CoV-2-mediated RAAS alteration; therefore, it is imperative to develop a conjugated approach to directional and hypertension therapy in a synergistic approach. Several reports established that hypertension and the RAAS axis bear the potential role in the pathogenicity of SARS-CoV-2 infection (Mancia et al. 2020; Jarari et al. 2016). Also, several studies and trials are underway on how the RAAS inhibitors could modulate the infectivity of SARS-CoV-2 (Zhang et al. 2020; Vaduganathan et al. 2020).

The identification and characterization of the specific drug target area and mechanism against SARS-CoV-2 remain an enigma to us, as is the role of antihypertensive drugs such as AREi and ARBs. Besides this, the possible mechanism behind the ACE2 modulator drugs or drug-induced modulation in K^+ and how they are involved in the possible lowering of the

SARS-CoV-2 infection is still an area that requires clarity. Along with the infection of SARS-CoV-2, simultaneous modulation of the RAAS axis occurs as it targets the ACE2 receptor, which in turn remains an integral part of the RAAS axis. While the COVID-19 virus manifestations persist, there is a modulated RAAS axis posing immediate or post-COVID-19 threats for a prolonged time. This observation has not been focused upon and needs in-depth investigation or otherwise may culminate into neglect of significance.

Possibly, along with the therapy against SARS-CoV-2, researchers must strategize solutions to the alteration in the RAAS axis simultaneously by providing an array of opportunities to reduce the severity and comorbidity in COVID-19 patients achieved through the designing of competent drugs. At this point, the possible drug target area against SARS-CoV-2 is still unclear to us. The same is true about the role of antihypertensive medications such as AREi and ARBs. The possible mechanism of ACE2 modulator drugs or drug-induced modulation in K⁺ and how they are involved in lowering the SARS-CoV-2 infectivity is still an area under investigation.

Data and materials availability Yes

Author contribution Mr. Rohit Sen designed the framework of the review article and prepared the manuscript. Dr. Devashish Sengupta provided inputs about the biochemical and drug-related aspects of the review. Dr. Avinaba Mukherjee supervised the entire manuscript preparation and hypothesized the possible drug target area.

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