Journal of Pharmaceutical and Scientific Innovation

www.jpsionline.com (ISSN: 2277–4572)

Research Article

THE RAS DISORDER AND INEFFECTIVE IMMUNE RESPONSES ARE RELATED TO THE SEVERITY OF COVID-19: THE RAS INHIBITOR AND THE ANTIVIRAL DRUGS CAN BE USEFUL

Sepideh Abbaszadeh, Pejman Molaei, Saeid Afshar, Fatemeh Bahrami Banan*

[1]Department of Molecular Medicine and Genetics, Research Center for Molecular Medicine, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran.

***Corresponding Author**: Department of Molecular Medicine and Genetics, Research Center for Molecular Medicine, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran. fbahramibanan@yahoo.com, Telephone: +989183187207

DOI: 10.37532/2277-4572.2023.12(4).252

Received date: 25-October-2023, Manuscript No: JPSI-23-1181973; **Editor assigned:** 29-October-2023, Pre-QC No. JPSI-23-1181973 (PQ); **Reviewed:** 18-November-2023, QC No. JPSI-23-1181973 (Q); **Revised date:** 9-December-2023, Manuscript No: JPSI-23-1181973 (R); **Published date:** 12-December-2023

ABSTRACT

SARS-CoV2 utilizes the Angiotensin-Converting Enzyme (ACE2) transmembrane receptor to infect the cell. ACE2 plays a pivotal role as one of the primary enzymes within the Renin-Angiotensin System (RAS), responsible for regulating the homeostasis of different organs. RAS hyperactivity, accompanied by an increase in the ACE/ACE2 ratio, leads disorders such as cardiovascular, pulmonary, and renal problems and uncontrolled inflammatory responses having been similarly observed in patients with COVID-19 too. Probably using the ACE2 as the receptor by SARS-CoV2 leads disturbance in RAS, that might be the cause of the destructive effects of the virus. On the other hand, humoral immunity plays a considerable role in the recovery of patients by producing antibodies against the viral particles, while inflammation response inducing cellular and innate immunity, have a negative effect. Therefore, what seems to affect the severity of the disease is the kind of the response of the immune system and the different ACE / ACE2 ratio in individuals. If during viral infection, before effective elimination of the virus by humoral immunity, the ACE / ACE2 ratio surpasses the usual amount, the deregulation of the system will be ineffective, and the destructive effects of RAS hyperactivity on the target organs will occur, the patient will experience the severe type of the disease, but if the virus is removed on time, a mild form will happen. Probably combination therapy with RAS inhibitors and the antiviral drugs that prevent viral proliferation can be useful.

Keywords: SARS-Cov2 infection, ACE2, RAS hyperactivity, immune response, RAS inhibitors.

INTRODUCTION

On December 30, 2019, severe pneumonia was first reported in Wuhan, China and it has quickly spread to all countries of the world [1]. It was then determined that the disease is caused by a novel virus named “SARS-CoV2” (Severe Acute Respiratory Syndrome-related Coronavirus 2) [2]. Although the mortality rate of the disease is estimated to be low, the high prevalence of the disease has increased the number of deaths due to the disease and has brought a global health crisis [1]. SARS-CoV and SARS-CoV2 have a high similarity in the genome sequence, and SARS-CoV2, like SARS-CoV, uses the ACE2 (angiotensin-converting enzyme 2) as the receptor to infect the body cells specially cells of the pulmonary system [3,4].

Studies have shown that spike glycoprotein of the SARS-CoV2 compared to the same glycoprotein in SARS-CoV has more affinity for ACE2 binding [5]. ACE2 is recognized as a key enzyme within the Renin-Angiotensin System (RAS) and its main functions including: regulating systemic vascular resistance, blood pressure, lung protection, fluid and electrolyte balance [6-10].

The components of this system interact with each other, and their effects maintain the optimal level of all components in a proper balance. Disorders caused by the system hyperactivity will cause symptoms that include ARDs (Acute respiratory distress syndrome), cardiovascular, and renal problems [11-13].

In this review, an attempt has been done to analyze the renin-angiotensin system and the interaction of its components, and had been shown disruption of this system in patients with COVID-19 is the main destructive factor. Therefore, by analyzing the disorder created by the virus, suitable treatment of COVID-19 can be suggested.

Renin-angiotensin system

The Renin-Angiotensin System (RAS) is one of the main mediators of various mechanisms in human body such as fluid, volume and electrolyte homeostasis and most importantly blood pressure. This system plays an important role in many organs including: heart, brain and kidney [14].

This pathway has many members that each of them has a specific task. ACE, ACE2, Angiotensin II receptor 1 (AT1R), Angiotensin II receptor 2 (AT2R), and Mas receptor (masR) are essential proteins in the RAS that interact with each other, thereby keeping the level of the system compounds in proper balance. The activity of angiotensin II / AT1R / ACE is in one direction, opposite of the activity of angiotensin 1-7 / ACE2 / AT2R / masR [11-13].

Angiotensinogen is converted to angiotensin I by Renin, then converted to angiotensin II, 1-9, and 1-7 under the effect of ACE, ACE2, and NEP. Having converted angiotensin II to angiotensin 1-7, ACE2 also inactivates it and prevents its overload [15-18].

AT1R activity is the opposite of AT2R and masR activity.

AT1R negatively adjusts the ACE2 by activating its downstream pathway, opposite of AT2R and masR activities, inhibiting these downstream pathways, and increase ACE2 expression [19-21].

In a healthy person, the interaction of these receptors causes the ACE / ACE2 ratio to be in the proper balance [19, 22]. Angiotensin II can bind to AT1R, AT2R, and angiotensin 1-7 can bind to AT1R, AT2R, and masR and stimulates the downstream pathways of these receptors. Angiotensin 1-7 has an agonist effect on AT2R and an antagonistic effect on AT1R. To balance the system, in addition to AT1R, angiotensin II binds to AT2R, and AT2R activity increasing ACE2 and masR expression, somewhat reducing the effects of AT1R downstream pathways [23-28]. ACE2 converts angiotensin II to angiotensin 1-7, binding to its receptors for more system adjustment [26, 27]. Therefore, under normal conditions, the ACE / ACE2 level remains at the appropriate balance, and an increase in the ratio from the reasonable amount indicates hyperactivity in RAS [19, 22, 25]. Figure 1 schematically shows the interaction of RAS components and their effects.

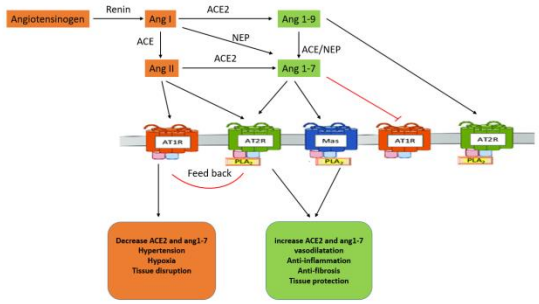

Figure 1. The interaction of RAS components and their effects.

Bradykinin (BK), which is a linear nonapeptide, is generated through the proteolytic activity of kallikrein on kininogens. Kallikrein is a serine proteinase and can be divided in two forms, tissue and plasma kallikrein [29]. discoveries showed that kallikrein–kinin have important functions in humans, consisting of anti-inflammatory and antioxidant agent in protection against cardiovascular, stroke and renal disease, and as a major drug targets for the treatment and management of several diseases such as stroke, vascular injury, heart failure and end-stage renal [30]. Recent studies revealed the downregulation of ACE2 and its enzymatic activity reduction are observed in the context of SARS-CoV infections as well as during inflammatory processes [31]. BK possesses two seven-span transmembrane receptors linked to G proteins, which are found in various mammalian tissues. Specifically, the B1R (B1 receptor) subtype typically exhibits low expression levels under normal circumstances but can be upregulated by treatments involving substances like LPS (lipopolysaccharide) and cytokines such as IL-1α, IL-1β, and TNF. Conversely, the B2R (B2 receptor) subtype is constitutively expressed in numerous organs. [32,33]. B1R, which exhibits sensitivity specifically to kinin metabolites lacking the C-terminal arginine residue, tends to be upregulated in immunopathological situations following the presence of cytokines and is subject to regulation by growth factors [34]. ACE2 demonstrates a greater affinity for BK in comparison to Ang I , and it has the capability to deactivate potent ligands of the B1R receptor in the lung, such as LDABK (Lys des-Arg9-BK) and DABK (des-Arg9-BK) [31, 35, 36]. Decreased expression of this protein by the novel virus hampers the inactivation of DABK [37]. The interaction between BK and B2R on the vascular endothelium leads to the production of various inflammatory factors, including NO, prostacyclin, and endothelium-derived hyperpolarizing [38]. Based on recent studies, B2R has an interaction with ACE2 directly, which ACE2 acts as allosteric enhancer [39]. Studies showed that suppressing the B2R and inhibition of plasma kallikrein activity has a strong effect in patients with COVID-19 and effectively prevent ARDS [29].

The similarity of the symptoms of the RAS hyperactivity with COVID-19 SYMPTOMS

In RAS, the ACE/angiotensin II / AT1R axis serves to activate the system, and the ACE2 / angiotensin1-7 / AT2R / masR axis acts to control the system. Finally, the activity of the two axes keeps an appropriate level of the ACE / ACE2 ratio [40]. An increase in this ratio from a certain level is a sign of activity of the ACE/angiotensin II / AT1R axis more than the normal [19, 41].

Having raised the level of angiotensin II and further activation of the AT1R downstream pathways, (RAS hyperactivity) causes high blood pressure, endothelial dysfunction, and ultimately congestive heart failure [42], vasoconstriction and Bronchoconstriction, inflammation, increased vascular permeability, fibrosis, ARDS progression and severe lung damage [43, 44], tubular cell hypoxia, apoptosis or deformation of mesenchymal-epithelial cells, capillary destruction, chronic hypoxia and fibrosis in the kidney [45], (figure2) and other destructive effects on other organs. Also, at the onset of diabetes, AT1R is activated, and AT2R is reduced, causing inflammation, narrowing of blood vessels, thrombosis, oxidative stress, and endothelial damage [46]. In all of these diseases, the ACE / ACE2 ratio is very high [19]. These symptoms are the same as seen in people with the severe type of COVID-19; the most important of them is ARDs [47-51]. The SARS-CoV2 use of ACE2 as the receptor for cell entry [52], induces downregulation of ACE2 receptor and losing its function [53], which accompanied by an increase in angiotensin II and further activation of the AT1R signaling pathway, performs ACE2 downregulation, increase the ACE / ACE2 ratio, and disturbs the RAS balance (Figure 2) [19].

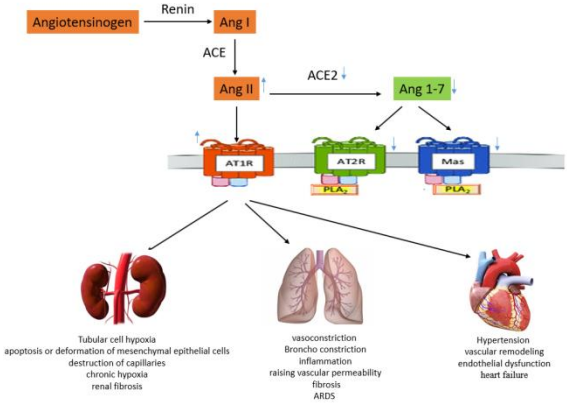

Figure 2. Effect of RAS hyperactivity on different organs

The responses of the immune system to the COVID-19

In COVID-19, many patients confront mild or no symptoms. However, some patients may experience severe symptoms such as lymphopenia and pneumonia with cytokine storm, inducing ARDS, organs failure, and eventually death [54]. During SARS-CoV2 infection, out of control immune response due to the hyper-activation of macrophages, monocytes, and neutrophils is seen, associated with decreased lymphocytes [55]. Cellular and humoral immunity have a viral role in all viral infections. In cellular immunity, activation of T helper 1 and T helper 17 caused exacerbates the inflammatory response and deterioration of the COVID-19 disease. One of the causes of exacerbation of inflammatory responses in the body is RAS hyperactivity, to accompany by the complement system activity. One of the signaling pathways of AT1R is releasing of inflammatory

cytokines and the differentiation of cd4+ to T helper 17 also, studies have shown that angiotensin II can affect inducing macrophage and neutrophil inflammatory response [56.57]. In contrast, angiotensin 1-7 with binding to MasR modulates inflammatory cytokine responses caused by the AT1R signaling pathway. Therefore, Angiotensin II/ACE/AT1R axis hyperactivity and an increase in the ACE/ACE2 ratio will be associated with a decrease in angiotensin 1-7 and an increase in angiotensin II, can lead releasing out-of-control of different inflammatory cytokines, called cytokine storm [56]. In contrast, in humoral immunity, first IgM and then IgG is produced against the SARS-CoV-2 to neutralize the viral particles. It is necessary to mention for both SARS-CoV and MERS-CoV infection, delayed or feeble in humoral response had been associated with deterioration of the disease**.** Due to the different effects of the type of immune response on the severity of the COVID-19 disease, t effective treatment methods have been suggested. In one method in China, for reducing lung injury in patients with COVID-19, tocilizumab has been used, reducing inflammation responses [54]. Also, the use of plasma of improved patients of COVID-19, containing antibodies against SARS-CoV2 particles, was effective in the recovery of other patients with COVID-19 [58,59]

Relation among vitamin D, RAS, and SARS-CoV2

Today, it is well established that there is a close relation between high blood pressure and Vitamin D-deficiency [60].

Studies showed that inhibition of vitamin D leads to an up-regulation of renin, while treatment with vitamin D results in a reduction of renin levels in the kidney also, the interaction of vitamin D with RAS have shown that vitamin D is a potent deregulator of endocrine glands for the RAS [61,62], primarily responsible for suppressing renin biosynthesis [60, 63]. One study found that mice lacking vitamin D receptors increased the production of renin and angiotensin II, eventually leading to high blood pressure and heart problems. The suppression of renin expression via vitamin D is independent of its effect on calcium metabolism and the mechanisms for measuring salt and volume and angiotensin II feedback regulation [63]. Hypovitaminosis D is seen to be common in kidney-failure patients and increases the risk of ARDS, as well as diabetes, cardiovascular events, and comorbidities These factors collectively contribute to the increased severity of the disease in COVID-19 patients. Evidence suggests that vitamin D decreases the severity of COVID-19 disease because it reduces the symptoms of RAS hyperactivity by inhibiting RAS and prevents tissue damage induced by immune responses of T helper 1 and excessive inflammation. However, it's necessary to pay attention, that vitamin D may decrease the memory B cells and inhibit the production of plasma cells, associating with the decrease of the level of secretion of antibodies and was determined in the suppression of renin cascade, analogues of vitamin D might have some advantages over the Ang II receptor blockers and ACEIs [61, 64-69].

Drugs inhibiting renin-angiotensin system in COVID-19

Two relevant groups of drugs are ACE Inhibitors (ACE-Is) and Angiotensin II Receptor Blockers (ARBs) that have effectively resolved the problems of all diseases created by RAS hyperactivity. ACE-Is reduce angiotensin II levels by inhibiting ACE, and ARBs inhibit AT1R signaling by blocking AT1R and inhibit RAS by this mechanism [70, 71]. In COVID-19 disease, initially, there appeared to a concern for the use of these drugs because the use of them is associated with an increased expression of ACE2, and will be accompanied by an increase in viral infection [72]. However, this possibility has not been proven, and no evidence the people are taking these drugs are at higher risk of SARS-CoV2 infection [44, 73]. Although one study in mice showed that increasing ACE2 expression raised the risk of SARS-CoV infection and respiratory symptoms, this study did not simultaneously examine the effect of ACE-I or ARB on disease severity [52, 74]. Even another study at Hobby Hospital in China, the mortality rate in patients with high blood pressure was 3.7% with ACE-I and 9.8% without medication [75]. Besides, the results of several studies show that the use of these drugs not only harmful but also effective in improving and reducing mortality [44].

Icatibant, as a specific antagonist of B2R, is a synthetic drug including 10 amino acids 76 and currently utilized for the symptomatic management of angioedema attacks associated with thermal injury. it's mechanism is independent from CYP450 (cytochrome P450) activity [36, 76-78]. ACEIs apply their therapeutic effects by inhibiting the conversion of ACE to ACE2; they also suppress the breakdown of BK, as a result increasing its activity [79]. More studies showed that icatibant can increased vascular permeability in mice [80]. The inhibition of receptor binding of BK is a practical method for managing acute attacks of Hereditary angioedema (HAE). Icatibant is a targeted and more specific treatment than other currently available treatment approaches [81].

CONCLUSION

the decrease in the ratio of active ACE2 to active ACE, seen in all diseases and symptoms induced by renin-angiotensin system hyperactivity disorder (19), is observed in COVID-19, too (82). the decrease in this ratio is the sign of RAS hyperactivity. Therefore, patients are more likely to experience this hyperactivity disorder during SARS-CoV2 infection. This issue and its resemblance to the symptoms and organs involved in COVID 19, with diseases caused by hyperactivity of the renin-angiotensin system, and the greater susceptibility of patients with these diseases to COVID-19 (70, 72), suggest that what has made SARS-CoV2 likely be a destructive body virus is a double disorder in the RAS and its hyper-activation by the virus in such patients.

On the other hand, the effectiveness of plasma therapy in the recovery of patients with COVID-19 shows that if the humoral immunity acts on time to eliminate the virus, it can be useful in improving patients. In contrast, RAS hyperactivity and further activation of cellular immunity lead to the worsening of the disease.

Therefore, what seems to affect the severity of the disease is the kind of the response of the immune system and the different ACE / ACE2 ratio in individuals. If the ACE / ACE2 ratio is higher than the reasonable amount during viral infection by RAS hyperactivity, the deregulation of the system will be ineffective, and the destructive effects of RAS hyperactivity on the target organs will occur, the patient will experience the severe type of disease. Therefore, if the humoral immunity removes the virus before the ratio crosses the reasonable amount, a mild form of the disease will develop. In patients with underlying conditions such as cardiovascular disease, diabetes, renal and pulmonary problems in which the RAS is hyperactive, the ACE / ACE2 ratio itself is high, and the virus infection doubles the increase, before the effective humoral immunity response. For this reason, these people are likely more prone to severe forms of the disease.

Since it seems the RAS hyperactivity during viral infection causes a detrimental effect on the body, likely, the use of ACE-Is or ARBs, which have been effective in solving the problems of all diseases caused by RAS hyperactivity can be effective in eliminating the destructive symptoms of COVID-19. It is possible that if the virus-induced renin-angiotensin system disorder is compensated on time by ACE-Is or ARBs, the viral infection itself will have a little destructive effect and inhibiting the AT1R signaling pathway until the humoral immunity responds to eliminate the virus, will be effective in preventing the disease from getting worse. However, reducing the rate of

viral infection is also reasonable in addition to compensating for RAS disorder. Therefore, combination therapy that regulates both RAS and disrupts the viral proliferation cycle appears to be more effective. Accordingly, combination therapy with ACE-Is or ARBs, inhibiting renin-angiotensin pathway activity, is not only safe in people with underlying disease or people without underlying disease, but along with antiviral drugs that prevent the virus from multiplying is also useful. And the side effects of ACEI including cough and ACEI-induced angioedema, antagonists of AT1R and identified as ARBs (angiotensin receptor blockers). BK is thought to play a cardio-protective role. However, icatibant could potentially impair cardiac function and decrease coronary blood flow.

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How to cite this article:

Banan F B, et al. *The RAS Disorder and Ineffective Immune Responses are Related to the Severity of Covid-19: The RAS Inhibitor and the Antiviral Drugs can be useful*. J Pharm Sci Innov. 2023;12(4):252

Source of support: Nil, Conflict of interest:
None Declared