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A Look into Possible New Treatment Modality For COVID - 19: ACE 2

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Abstract

Many articles about COVID 19 have mentioned various experimental drugs but nowhere it has been mentioned about any new research on ACE 2 (Angiotensin converting enzyme 2), which is a receptor for coronavirus, in the direction of curbing it. Hereby a logically deduced & scientific study backed analysis of a group of drugs affecting the ACE2 system is presented. ACE2 is an integral part of the pathogenic mechanisms & disease progression of COVID-19 & up regulation of ACE2 levels leads to significant reduction in morbidity & mortality of ARDS. SARS-CoV-2 binds to & down regulates this protective ACE2 & thus leads to the acute lung injury associated with it. Hence ACE 2 up regulation maybe the way to defeat this pandemic which has the whole of humanity in its grip.

Keywords: Coronavirus; Angiotensin Converting Enzyme 2; ACE2 enzyme; Coronavirus receptor; COVID-19; Angiotensin receptor blockers; Angiotensin-Converting Enzyme Inhibitors

Introduction

Coronavirus is the new pandemic which has the whole of humanity tied all hands together in its fighting. Coronaviruses are pleomorphic, single stranded RNA viruses. They measure about 100-160 nm in diameter [1]. Their name is derived from the unique club like projections on their envelope. The unique feature of this virus family is its genome. Coronavirus has the largest genome amongst all the RNA viruses [2]. Human infections are caused by two genera-Alphacoronaviruses & Betacoronaviruses. SARS-CoV& MERS-CoV, the two old epidemic causing agents of this family, belong to betacoronaviruses. The novel CoVID-19 strain is identified as a new strain of Betacoronavirus itself from group 2B. It has nearly 70% genetic similarity with SARS-CoV [3]. The cells of respiratory tract are infected by COVID through angiotensin converting enzyme 2 receptor [4], which is also implicated in ARDS (acute respiratory distress syndrome) pathogenesis. Hence lot of work needs to be directed in this direction.

Epidemiology

Coronavirus infections are quite prevalent throughout the world, with serum antibodies being demonstrated in> 80% adult populations [1]. In the 2003 SARS-CoV outbreak, more than 8,000 people were infected. 10% of the infected people died [4].

The 2012 MERS-CoV (Middle East respiratory syndrome coronavirus) outbreak was slightly limited in its spread. About 2,468 cases of MERS-CoV infection have been diagnosed. 851 fatalities were there giving a mortality rate of approximately 34.5% [5].

In December 2019, a pneumonia outbreak was reported in Wuhan, China. The organism was named 2019-nCoV by WHO. It was renamed SARS-CoV-2 by the International Committee on Taxonomy of Viruses. As of recent statistics, there are about 2,28,000 confirmed deaths and more than 32,00,000 confirmed cases in this coronavirus pandemic. The worldwide restrictions in travel, events & the popular social distancing are all a result of this novel COVID-19 disease.

The mode of transmission is droplet infection, although feco-oral route was also a suggested mode of transmission in the SARS cluster of cases.

Pathogenesis

Coronaviruses causing common cold infect ciliated epithelial cells in nasopharynx via aminopeptidase N receptor (group 1) or sialic acid receptor (group 2). The cytokines produced damage the ciliated cells [6]. One interesting detail is that the cells of respiratory tract are infected by COVID through angiotensin converting enzyme 2 receptor [4]. *In-vitro* studies demonstrate CD209L (L-SIGN) as an alternate possible receptor.

Clinical features

Include fever (85%), dry cough (66%), fatigue, breathlessness, muscle & joint pains, sore throat or headache. Complications include severe pneumonia, acute respiratory distress syndrome, sepsis, septic shock and death. The usual incubation period is 1-14 days; commonly being 5 days.

Angiotensinogen secreted from liver is converted to angiotensin I via renin (secreted by JG cells of kidney). Angiotensin I is converted to angiotensin II mainly by angiotensin converting enzyme (ACE). An insignificant amount of angiotensin II is also produced by chymase enzymes (non-ACE pathway), which assumes importance when ACE is inhibited by drugs like enalapril, captopril (ACE inhibitors). Angiotensin II acts on AT1 (main) & AT2 receptors. AT1 causes vasoconstriction & stimulation of aldosterone release. This vasoconstriction as well as aldosterone mediated salt & water retention causes a rise in blood pressure (Figure 1).

Angiotensin converting enzyme 2 as a receptor for coronavirus

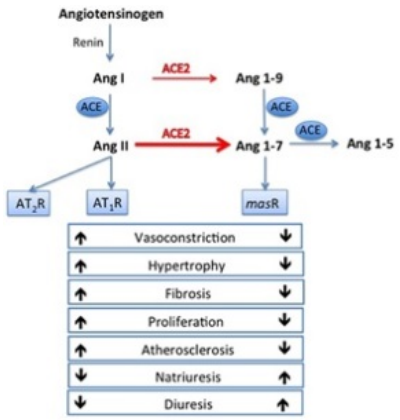

Figure 1: Renin angiotensin system & various enzymes involved [7].

Angiotensin-converting enzyme 2 (ACE2) shares some homology with angiotensin-converting enzyme (ACE) but it is uninhibited by ACE inhibitors. The main role of ACE2 is the degradation of Ang II resulting in the formation of angiotensin 1–7 (Ang 1–7), which opposes the actions of Ang II. Ang (1-7) binds and results in activation of Mas receptor (G-protein coupled receptor) [8]. It also acts on angiotensin II receptor type 2(AT2 Receptor). Increased Ang II levels up regulate ACE2 activity. In ACE2 deficient mice, Ang II levels are nearly double that of wild-type mice, while Ang 1–7 levels are almost nil. ACE2 may have a beneficial role in many diseases such as hypertension, diabetes, and cardiovascular disease where its expression is decreased [9].

ACE2 is the entrance point of selected coronavirus strains which include HCoV-NL63, SARS-CoV and SARS-CoV-2, the virus causing the COVID-19 pandemic [4]. Even the mutants of site of activity of ACE2 have no difficulty in binding to SARS-CoV S protein [10]. This proves that ACE2 catalytic activity isn't needed in receptor functioning. It has been shown that inhibitors lead to profound conformational changes in the enzyme's active sites [11]. This finding raises the possibility of a mechanism to interfere with the initiation of infection, but it is also seen that there is no effect of inhibitor on S-protein binding or receptor functioning of ACE2 [12]. ACE2 is needed for SARS infections *in-vivo* [13]. ACE2-knockout mice when infected with SARS-CoV were found to have resistance to the viral infection. Even the virus titers in the lungs from infected ACE2 knockout mice were 105x lesser than those of wild type mice [13].

This finding must be further evaluated upon. One may deduce that decreasing the levels of ACE 2 should help in reducing Coronavirus infection, as it is the hypothesized entry point. However, coronavirus infections ultimately lead to a decrease in the level of ACE 2 & that decrease in ACE 2 is indeed responsible for the acute lung injury which befalls the severely ill COVID patient [13]. Patients with sepsis/ARDS have shown higher levels of ACE/Ang II. In genetic studies it has been found that D (deletion) allele of ACE gene leads to high ACE/AngII levels. Numerous articles have suggested that ACE-D allele is related with mortality in ARDS [14].

Loss of ACE2 expression results in increased permeability of vessels, increased lung edema, neutrophil accumulation & worsened functioning of lung. Hence, ACE2 has quite a protective role in acute lung injury. Pulmonary circulation is an important target for the RAS (renin–angiotensin system) in lungs. Ang II acts on AT1 Receptor & leads to pulmonary vasoconstriction (in response to hypoxia) which inturn leads to pulmonary oedema. In addition, vessel wall permeability is also enhanced by Ang II action on AT1 receptors. AT2 receptor exerts opposite effects, & as described before, AT2 is the receptor for Ang (1-7), a by-product of ACE2 [15]. In short ACE2 leads to the production of Ang (1-7), which exerts protective effects on lung vasculature via AT2 receptor. ACE2 inhibits AngII, hence the pathogenic effects of AngII in ARDS are stopped. Hence this is also a proposed mechanism for the ARDS protective effect of ACE2.

It has been shown that ARDS in mice is controlled by blockade of RAS (renin–angiotensin) pathway or the injection of catalytically-active human recombinant ACE2 protein [14]. ACE is present in the entire network of lung capillaries. Only 20% of capillaries of rest of organs express ACE [16]. Hence, Ang I to Ang II transformation occurs abundantly in the lungs by the predominant ACE in lung vasculature. This predominant conversion leads to the rapid vasoconstriction of lung vasculature which leads in turn to severe ventilation/perfusion mismatching.

The clara cells & type-II alveolar epithelial cells are the primary producers of ACE2 [17]. Epithelium injury is critical in ARDS pathogenesis. Hence in ARDS, the ACE 2 secreting function of epithelium is also lost. This also shows that decrease in ACE2 has a role in ARDS pathogenesis (Figure 2) [18,19].

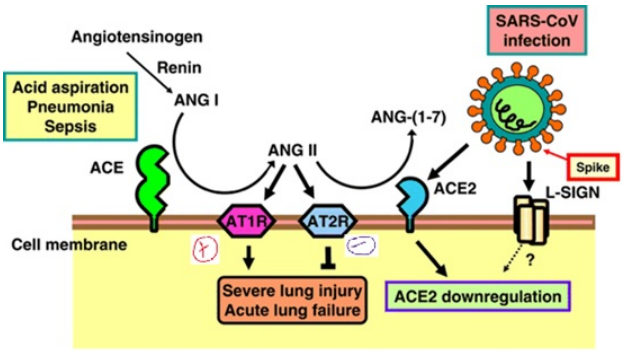

Figure 2: RAS in acute lung injury & SARS-CoV infection. Acute lung insults lead to increased Ang II production by ACE. Ang II acts on Angiotensin 1(AT1) receptor which leads to progression of the injury. ACE2 & AT-2 receptor (Ang II type 2 receptor) inhibits this mechanism & protect the lung from ARDS. SARS-CoV binds through its spike protein to ACE2 (or? L-SIGN receptor also) & leads to the down-regulation of this protective ACE2, hence leading to severe lung injury & acute lung failure [20].

Why SARS-COV triggers such severe lung disease, whereas the other corona strains don't, is a mystery. The virus replication burden is shown to determine the severity of the infection. RAS (Renin Angiotensin system) is involved in the SARS pathogenesis, with ACE2 being a critical receptor for SARS infections *in-vivo*. There is one interesting observation, even before ACE2 was identified as SARS-receptor, 2D echocardiographic measurements showed decreased cardiac contractility [21]. Meanwhile ACE2 deficient mice had also demonstrated reduction in cardiac contraction. Definitely the decrease cardiac function was attributed partially to other factors also including

the systemic inflammatory response. Even then this finding shows the possibility that it may have been the reduction of ACE2 by the SARS virus which lead to impairment of cardiac contraction, just like it was impaired in the ACE2 deficient mice. The viral receptor down regulation as a result of viral multiplication maybe visualized in others viruses as well. CD4, a receptor for HIV, internalizes with HIV gp120 leads to internalization of the CD4 receptor which in turn disrupts the immunity mediating functions of the CD4. Similarly, measles-haemagglutinin down regulates CD46 (measles receptor) & leads to impairment of complement and immune system. Hence a similar reduction of ACE2 by the SARS-CoV maybe the mechanism of the ARDS pathogenesis by this agent.

ACE inhibitors & ARBs (Angiotensin receptor blockers) have led to increased ACE2 levels in rodent studies. A systematic review and meta-analysis found that "use of ACE inhibitors was associated with a significant 34% reduction in risk of pneumonia compared with controls" [22] & "The risk of pneumonia was also reduced in patients treated with ACE inhibitors who were at higher risk of pneumonia, in particular those with stroke and heart failure. ACEI effectively depresses pulmonary arterial hypertension, block the development of ARDS, and has protective effects on pulmonary capillary endothelia [23]. Use of ACE inhibitors is associated with reduction in pneumonia related mortality."

Khan et al. [23] conducted a phase II trial to examine safety & efficacy of GSK2586881, which is a recombinant human ACE2 (rhACE2), in ARDS patients. They showed that GSK2586881 was safe & didn't cause much hemodynamic alterations. Twice-daily GSK2586881 infusions resulted in rapid Ang II level decline & an increase in Ang (1-7) & Ang (1-5) level. There was a decrease in IL-6 concentration also. IL-6 levels are significantly higher in ARDS patients [24].

Conclusion

The coronavirus pandemic has brought about a lot of implications, not just in medicine, but for humanity as a whole. We all have stood up now as one, giving up all divisions of caste & creed in the fight against coronavirus.

After understanding this pathogenic mechanism of ACE 2 enzyme and its role in ARDS due to coronavirus, research has to be progressed in this direction. Trials using recombinant human ACE 2, ACE inhibitors or even ARBs (aldosterone receptor blockers) are hence absolutely warranted in this fight against the coronavirus as ACE inhibitors & ARBs also increase the levels of ACE2. ACE2 as described above is an integral part of the pathogenic mechanisms & disease progression of COVID-19. As demonstrated by analysis of various studies, up regulation of ACE2 levels leads to significant reduction in morbidity & mortality of ARDS. Moreover, it is shown that SARS-CoV binds to & down regulates this protective ACE2 & thus leads to the acute lung injury. Hence ACE 2 up regulation maybe the way to defeat this pandemic which has the whole of humanity in its grip. It is sincerely hoped that further research in this direction powers us to overcome this coronavirus scare & we come out of this as better individuals & most importantly, better humans.

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