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Urgent need for evaluating agonists of angiotensin-(1-7)/Mas receptor axis for treating patients with COVID-19

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A B S T R A C T

ACE2 is a receptor of entry of SARS-CoV-2 into the host cells, and its upregulation has been implicated in increasing susceptibility of individuals to this infection. The clinical picture of COVID-19 suggests a role of ACE2 blockade, rather than its overexpression, in causing the pathogenesis. ACE2 blockade results in increased angiotensin II activity with simultaneous hampering of functions of angiotensin-(1-7)/MasR axis. Acute respiratory distress due to interstitial pulmonary fibrosis, cardiomyopathy and shock reported in COVID-19 patients can be explained by imbalanced angiotensin II and angiotensin-(1-7) activities. Failure of angiotensin II type 1 receptor blockers to control the severity of SARS-CoV-2 infections indicates the importance of simultaneous induction of angiotensin-(1-7)/MasR axis for correcting pathological conditions in COVID-19 through its anti-fibrotic, anti-inflammatory, vasodilatory, and cardioprotective roles. MasR agonists have also shown organ protective effects in a number of animal studies. Unfortunately, these agonists have not been tested in clinical studies. Their evaluation in seriously ill COVID-19 patients is urgently warranted to reduce mortality due to infection.

Introduction

New modalities for managing seriously ill patients with COVID-19 are of the utmost importance, considering the increasing spread and number of deaths due to the SARS-CoV-2 infections worldwide. Unfortunately, lopinavir-ritonavir treatment has failed to demonstrate significant clinical improvement and reduce mortality in patients with serious COVID-19 infections (Cao et al., 2020). Although drugs like hydroxychloroquine, azithromycin and ivermectin have been proposed to improve viral clearance (Caly et al., 2020; Ferner and Aronson, 2020), sufficient evidence for their efficacy in COVID-19 patients is warranted. The lack of effective treatment modalities for managing severe illness has caused a large number of deaths, even in developed countries with advanced healthcare facilities.

Angiotensin-converting enzyme 2 and COVID-19

Angiotensin-converting enzyme 2 (ACE2) acts as a receptor for SARS-CoV-2 entry into the cells by interacting with S protein of the virus. Interaction between ACE2 and S protein has been shown to be responsible for infectivity as well as severity of the infection.

Individuals with hypertension, cardiovascular diseases (CVD) or diabetes showing higher expression of ACE2 have been shown to be at a higher risk of developing serious infections with SARS-CoV-2 (Huang et al., 2020). ACE2 upregulation has also been shown to occur upon administration of ACE inhibitors (ACE-I)/angiotensin II type-I receptor blockers (ARBs), which are commonly used for managing these conditions (Ferrario et al., 2005; Furuhashi et al., 2015), predisposing those who take them to a higher risk of infection with SARS-CoV-2. Individuals with COVID-19 have been also shown to have higher ACE2 levels correlating with viral load (Liu et al., 2020), suggesting its role in COVID-19 pathogenesis. This is in contrast with the earlier reports about ACE2, which have shown its role in reducing inflammation (Fu et al., 2017). Based on the controversial opinions about continuing the medications that up-regulate ACE2 levels, guidelines recommend their continuation because there is a lack of evidence of benefit after discontinuation. Contrarily, few reports have highlighted potential benefits of these drugs in COVID-19 patients (Meng et al., 2020; Vaduganathan et al., 2020). However, convincing benefits of using these agents are lacking. In one of the reports on COVID-19, mortality was reported in 36.8% patients on ACE inhibitors/ARBs versus in 25.6% individuals without their use (Guo et al., 2020). The role of ACE2 polymorphisms in increasing the risk of SARS-CoV-2 infection has been suggested among Asian populations (Fang et al., 2020). However, the role of the polymorphism is

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questionable, considering the increasing numbers of deaths even in Western countries. Further investigations for understanding the interactions between SARS-CoV-2 and the renin-angiotensin system are required for devising effective management strategies.

Deleterious effects mediated by angiotensin II

ACE2 is a key regulatory enzyme in the system responsible for degradation of bioactive angiotensin II to angiotensin-(1-7). Angiotensin II has been shown to be the culprit in hypertension, CVD, diabetes, etc. Angiotensin II increases blood pressure through its action on the AT1 receptor (AT1R) expressed in renal and cardiovascular systems. Activation of the receptors expressed in human lung tissues has been reported to induce pulmonary fibrosis (Bullock et al., 2001). It has been shown to be involved in promoting tissue remodelling through formation of reactive oxygen species (Dikalov and Nazarewicz, 2013). Angiotensin II type 2 receptors (AT2R), in contrast to AT1R, exert vasodilatory effects. However, they show lower tissue expression in adults (Kaschina and Unger, 2003), indicating their limited role in countering the effects of AT1R.

Beneficial effects mediated by angiotensin (1-7)/Mas receptor

In addition to causing angiotensin II degradation, ACE2 exerts a cardioprotective role by increasing angiotensin-(1-7) levels. Angiotensin-(1-7) binds to the G-protein-coupled Mas receptor (MasR) to oppose deleterious effects elicited by angiotensin II (Savergnini et al., 2010). It has been shown to exert anti-hypertensive and cardioprotective actions through vasodilatory and antiarrhythmic effects (Santos, 2014). It has also shown anti-inflammatory and anti-fibrotic effects and has been shown to inhibit pro-inflammatory cytokines like TNF-α and IL-6 (Rodrigues Prestes et al., 2017). Moreover, it increased insulin secretion through improvement in pancreatic β-cell function in mice (Sahr et al., 2016). It also downregulated reactive oxygen species, protecting different cells from injury (Gwathmey et al., 2010). Angiotensin-(1-7) was reported to counteract the haemodynamic abnormalities in a clinical study undertaken in obese individuals (Schinzari et al., 2018). Different MasR agonists – like AVE 0991, hydroxypropyl β-cyclodextrin (HPβCD)/Angiotensin-(1-7), cyclic angiotensin-(1-7), CGEN-856 and CGEN-857– have been shown to exert protective effects when tested preclinically (Povlsen et al., 2020). The agonists were reported to possess antihypertensive and cardioprotective activities with higher in-vivo stability than that of angiotensin-(1-7) in animal studies (Savergnini et al., 2010). Clinical trials for evaluating angiotensin-(1-7) have shown it to be safe, well tolerated and devoid of any dose-limiting toxicities (Rodgers et al., 2006). TXA127, a pharmacological formulation of angiotensin-(1-7), has been granted orphan drug status by the FDA for the treatment of a number of conditions like pulmonary arterial hypertension, Duchenne muscular dystrophy, etc. (Drugs, 2020). Unfortunately, clinical studies for generating safety data on the other agonists are lacking.

Possible role of imbalanced effects of angiotensin II and angiotensin-(1-7)/MasR in mediating pathogenesis of COVID-19

The course of COVID-19 has been divided into three clinical stages: asymptomatic, upper respiratory tract involvement and progression to acute respiratory distress syndrome (ARDS) (Mason, 2020). Around 20% of patients with COVID-19 progress to stage 3, with a mortality rate of around 3-4%. Serious infections mainly occur in elderly patients with underlying comorbidities (Huang et al., 2020; Wang et al., 2020). Clinical findings in COVID-19 patients mainly point to increased activity of angiotensin II and the corresponding lack of angiotensin-(1-7) activity suggesting a role of ACE2 blockade in its pathogenesis. Elevated serum angiotensin II levels correlating with the viral load have been reported in COVID-19 patients (Liu et al., 2020).

Unfortunately, no reports regarding angiotensin-(1-7) levels in these patients are available. However, low angiotensin-(1-7) levels have been observed in bronchoalveolar lavage fluid in ARDS in animal studies (Wosten-van Asperen et al., 2011). Hence, studies are required to assess levels of angiotensin-(1-7) in COVID-19 to understand its role in the pathology. Old age had been shown to be associated with increased expressions of angiotensin II and AT1R and decreased expression of MasR (Yoon et al., 2016). This might explain the accentuation of pathologies in old age leading to severe infections. Blockade of angiotensin II activity through AT1R by ARBs has not shown much protection against the severity of infection, indicating limited protection offered through activation of AT2R by angiotensin II. It also stresses the importance of induction of angiotensin-(1-7)/MasR axis for controlling disease severity.

The severe infections have been associated with ARDS, cardiomyopathy, shock, and renal dysfunction (Wang et al., 2020; Phua et al., 2020). Patients with COVID-19 present with pneumonia and show loose interstitial fibrosis in lung tissue on histopathological examination (Zhang et al., 2020). High mortality rate has been reported in patients with acute respiratory failure and interstitial lung diseases requiring mechanical ventilators (Gungor et al., 2013). Around 97% of patients with COVID-19 requiring mechanical ventilation were reported to die in a study conducted in Wuhan (Ruan et al., 2020), indicating the need for anti-fibrotic agents to control pulmonary fibrosis in these patients. ARDS in COVID-19 has also been shown to be associated with neutrophilia and coagulation dysfunctions (Xie et al., 2006). In addition to contributing to fibrosis, angiotensin II has been shown to induce neutrophil accumulation (Nabah et al., 2004) and microvascular thrombosis (Senchenkova et al., 2010). Contrarily, angiotensin-(1-7)/MasR axis has been shown to inhibit pulmonary fibrosis (Meng et al., 2015), induce apoptosis of neutrophils (Reyes-Engel et al., 2006) and protect from thrombosis (Zhou et al., 2020). Myocardial injury has also been shown to be significantly associated with fatal outcomes of COVID-19. Inflammation is thought to be a potential mechanism for myocardial injury, causing cardiac dysfunction and arrhythmias (Guo et al., 2020). Protective effects of angiotensin-(1-7) on cardiac arrhythmias have been demonstrated by in vivo experiments in rats (Joviano-Santos et al., 2016). Inflammation and cytokine storm, which have been shown to contribute to shock in COVID-19 patients (Xu et al., 2020), indicate the possible protection of patients through the anti-inflammatory effects of angiotensin-(1-7)/MasR axis by reducing pro-inflammatory cytokines (da Silveira et al., 2010).

Possible organ protection through activation of angiotensin-(1-7)/MasR axis

The beneficial effects of angiotensin-(1-7)/MasR axis demonstrate its therapeutic potential to counter pathologies reported in patients with COVID-19. Patients with mild disease confined mainly to the upper respiratory tract just require conservative symptomatic therapy. However, patients in stage 3 disease presenting with hypoxia and pulmonary infiltrates need rigorous management and need to be evaluated for treatment with angiotensin-(1-7)/MasR axis agonists for reducing mortality. Interestingly, ACE2 and MasR have been shown to be expressed in the same tissues (Ferreira et al., 2010), indicating the protective role of MasR agonists in controlling the effects of ACE2 blockade in organs affected by COVID-19. Agonists of angiotensin-(1-7)/MasR axis have been reported to exert the Angiotensin-(1−7) mimicking effects in different organs like blood vessels, brain, kidney and neuronal tissues (Povlsen et al., 2020). Such organ-specific effect is likely to be lacking if soluble ACE2 is used for treating COVID-19. Treatment with soluble ACE2 has been shown to reduce angiotensin II levels and increase angiotensin-(1-7) levels in a clinical trial on patients with ARDS (Khan et al., 2017). However,

these effects are likely to occur at systemic levels, as evident from the lack of the clinical benefits reported in the trial (Khan et al., 2017). Hence, soluble ACE2, although it might block SARS-CoV-2 infections in the early stages as shown in a recent publication (Monteil, 2020), would have limited efficacy in severely ill COVID-19 patients as it would lack organ-specific effects.

Possible effect of age and gender on ACE2- angiotensin-(1-7)/MasR axis

Interestingly, older animal studies have shown lower ACE2 expressions (Yoon et al., 2016), contradicting the findings of higher susceptibility of elderly individuals to severe infections. However, no age-dependent changes in ACE2 levels were observed in a study conducted in humans (Schouten et al., 2019). Old animals were also found to have lower expression of MasR. However, AVE 0991 has been shown to exert a greater protective effect in older animals (Zheng et al., 2014), indicating possible effectiveness of the agonist in older individuals with COVID-19. Higher ACE2 levels were also reported in males with different co-morbidities (Anguiano et al., 2015; Soro-Paavonen et al., 2012). Males had been shown to have a higher vascular and renal sensitivity to angiotensin II compared with females, possibly explaining their higher frequency of severe SARS-Cov-2 infections (Toering et al., 2015). Functionality of the renin-angiotensin system has been shown to be influenced by gender and sex hormones (White et al., 2019). Although angiotensin-(1-7) levels have also been shown to vary with gender of animals, the protective effects of AVE 0991 have been demonstrated in both male and female animals (da Silveira et al., 2010).

Conclusion

Although higher ACE2 expression has been implicated in increasing the susceptibility of individuals to SARS-CoV-2 infections, the severity of infection is likely to be caused by blockade of ACE2 actions rather than its overexpression, if the clinical picture of COVID-19 is considered. ACE2 blockade is likely to lead to excessive levels of angiotensin II, along with deficiency of angiotensin-(1-7)/MasR axis. Failure of ARBs to control the severity of SARS-CoV-2 infections suggests the need for simultaneous induction of angiotensin-(1-7)/MasR axis for controlling disease severity. The mechanism of action of angiotensin-(1-7)/MasR axis indicates its potential for countering organ-specific adverse events occurring due to ACE2 blockade in COVID-19 patients. Despite the multiple reports on the beneficial effects of oral and injectable MasR agonists in animal models, they have not been clinically tested. The crisis condition of the SARS-CoV-2 infections and ever-increasing number of deaths caused by it warrant their urgent evaluation in seriously ill COVID-19 patients.

Conflict of interest

No conflict of interest to declare.

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Ethical approval

Approval was not required.

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