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A suggestion of using Ang-(1-7) and/or GLP-1 receptor agonists in high mortality patients with COVID-19

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Abstract

Currently, the emergence of a novel human corona virus, SARS-CoV-2, has become a global health concern causing severe symptoms. Angiotensin-converting enzyme 2 (ACE2) was intensively studied in the early 2000's because it binds with the spike protein of corona viruses SARS-COV and HCoV-NL63. This interaction is mediated by the ras-binding domain (RBD) of the spike protein, and is believed to be the pivotal event in the membrane fusion process. Recently, ACE2 has come back to the spotlight amid the outbreak of another deadly coronavirus, SARS-COV-2 (formerly 2019-nCoV). ACE2 is an integral component of the renin-angiotensin system (RAS). It is highly expressed in the vasculature, the kidney, lungs, and heart where its actions on peptide signals balance and offset those of ACE. The loss of ACE2 appears far more important in the development and progression of some cardiovascular diseases (CVD). There is a noticed increase of some inflammatory mediators as Lactate dehydrogenase (LDH), ferritin and C-reactive protein (CRP) with low neutrophile count in patient with SARS-CoV-2(COVID-19). There is significantly different clinical features between COVID-19-caused and non-COVID-19-caused pneumonia, especially in term of lymphocytopenia and organ injury. Notably, correlation analysis demonstrates that tissue damage in COVID-19 patients is attributed to virus infection itself rather than uncontrolled inflammatory responses. We therefore shed the light on all available information about the treatment of the cases, especially critical cases to decrease the mortality rate and maintain some important mediators within their important limits to give a great chance for the body and immune system to counteracts and eradicates the virus without further complications by a symptomatic treatment of COVID-19. Among our suggestions are Ang-(1-7) and/or GLP-1 receptor agonists as will be discussed in this short communication.

Introduction

A novel corona virus (SARS-CoV-2) has recently developed from China with a total of 1,773,084 confirmed cases and 111,652 total deaths by 10:00 CET 13 April, 2020 all over the world [1]. ACE2 is considered one of the targets of this novel corona virus. It is highly expressed in the kidney, the endothelium, the lungs, and in the heart. ACE2 directly antagonizes the vasoconstrictive and pro-oxidative effects of Ang-II by enhancing its degradation and increasing the production of Ang(1–7) from Ang-II [2]. As such, increased plasma and myocardial Ang-II levels have been attributed to reduced metabolism of plasma Ang-II due to absence or deficiency of ACE2 [3,4]. ACE2 deficiency is associated with up-regulation of putative mediators of atherogenesis, such as cytokines and adhesion molecules. Mechanistically, loss of ACE2 may also trigger activation of the myocardial NADPH oxidase system, increased production of superoxide, and activation of matrix metalloproteinases, leading to further adverse myocardial remodeling and dysfunction [5].

Pulmonary ACE2 also appears to have a role in regulating the balance of circulating Ang II/Ang (1–7) levels. Ang II induces pulmonary vasoconstriction in response to hypoxia, which is important in preventing shunting in patients with pneumonia or lung injury [6]. Locally increased Ang II production also triggers increasing vascular permeability facilitating pulmonary edema [7].

High Ang-II levels in COVID-19 infection

Once COVID-19 binds with ACE2, this leads to deficiency of ACE2 activity and increasing of Ang-II (a component of RAS, a major trigger of myocardial fibrosis) with decreasing of Ang-(1-7) production. It acts by stimulating pro-inflammatory cytokine secretion from fibroblasts. *In vitro*, angiotensin II induced much greater secretion of interleukin 6 protein (IL-6) and tumor necrosis factor-alpha (TNF-α) secretion in co-cultures of cardiomyocytes and fibroblasts than in cultures of fibroblasts alone, suggesting that paracrine action from cardiomyocytes plays an important role in the production of proinflammatory cytokines in fibroblasts [8]. The major physiological functions of Ang II are mediated by angiotensin II receptor type 1 (AT1) receptor [9,10]. In pathological conditions, activation of this receptor induces deleterious effects, such as vasoconstriction, fibrosis, cellular growth and migration, and fluid retention [11,12].

Disruption of ACE2 was able to accelerate cardiac hypertrophy and shortened the transition period to heart failure in response to pressure overload by increasing local Ang II [13]. Recently, it has been demonstrated that loss of ACE2 enhances the susceptibility to myocardial infarction, with increased mortality, infarct expansion and adverse ventricular remodeling [14]. In keeping with these genetic findings, pharmacological inhibition of ACE2 exacerbated cardiac hypertrophy and fibrosis in Ren-2 hypertensive rats [15]. On the other hand, cardiac overexpression of ACE2 prevented hypertension-induced cardiac hypertrophy and fibrosis in spontaneously hypertensive rats

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and in Ang-II-infused rats [16,17]. Indeed, transfection of Lenti-ACE2 (lentivirus containing ACE2 cDNA) or Ad-ACE2 (recombinant adenovirus carrying the murine ACE2) into the surrounding area of the infarcted myocardium was protective against pathological remodeling and cardiac systolic dysfunction in a rat model of myocardial infarction [18,19]. This effect was associated with decreased expression of Ang II and increased expression of Ang-(1–7) [19].

Angiotensin(1-7) and COVID-19 infection

Attachment of coronavirus with ACE2 leads to low Ang-(1-7) levels, as ACE2 is responsible for production of Ang-(1-7) from Ang-II. Ang-(1–7) showed significant attenuation of the DNA synthesis and proliferation of cancer cells. The antiproliferative effect of Ang-(1–7) was mediated by its receptor Mas and inhibition of the ERK1/2 pathway. Neither the blockage of AT1 nor AT2 succeeded in inhibiting the action of Ang-(1–7). In keeping with these data, the antiproliferative effect of Ang-(1–7) was observed in human A549 lung tumor xenograft growth along with a marked decrease in the vessel density in mice through a mechanism involving cyclooxygenase-2 (COX-2) [20,21]. This antiproliferative effect especially in lung cells can be useful in controlling COVID-19 pulmonary cases.

COVID-19 and kidney diseases

COVID-19 results in loss of balance between ACE2/ACE. Loss of balance between ACE2/ACE expression has been found in kidney biopsies from patients with type 2 diabetes and IgA nephropathy (IgAN), which suggests a shift toward intrarenal synthesis of Ang II and reduced Ang-(1–7). Acquired or genetic ACE2 deficiency and enzymatic blockade of ACE2 exacerbate renal damage and albuminuria in experimental models caused by Ang II and endothelin-1 downstream. Elevation of plasma levels of Ang-(1–7) can result in renoprotective effects through the modulation of oxidative stress, inflammation, and fibrosis at renal tissue [22].

GLP-1 receptor and COVID-19 infection

Glucagon-like peptide-1 receptor (GLP-1R) is also widely expressed in lungs [23,24]. Diabetes alters microvascular function in the vascular beds of organs, including the lungs. Cardiovascular complications of pulmonary vascular affectation may be a consequence of the overactivation of the vasoconstrictive and proliferative components of RAS. It has been reported that pulmonary physiology and surfactant production is improved by the GLP-1R agonist in a rat model of lung hypoplasia [24]. Interestingly, several recent clinical and experimental studies appear to indicate that GLP-1 exerts both anti-inflammatory and anti-atherogenic actions. For example, GLP-1 treatment in Type 2 diabetes (T2D) patients is associated with beneficial effects on a number of established CVD biomarkers, including high sensitivity C-reactive protein (hs-CRP) and plasminogen activator inhibitor-1 (PAI-1), which are important in atherosclerosis development [25]. Iwai *et al.* [26] found that GLP-1 inhibited the lipopolysaccharide LPS-induced increase in IL-1β in cultured cortical astrocytes and concluded that GLP-1 may be a modulator of inflammatory responses in the central nervous system, and likewise GLP-1 inhibited cytokine secretion and promoted survival after LPS-induced systemic inflammation in rats [27]. Thus, the present knowledge suggest that GLP-1 displays antiinflammatory effects and considering the fact that GLP-1R is present in the lung, we hypothesize that systemic GLP-1 might attenuate acute lung disease in a mouse model of obstructive pulmonary disease.

Suggested strategy to alleviate COVID-19 emergency symptoms

Angiotensin-(1–7) has a short plasma half-life and is rapidly degraded in the gastrointestinal tract when given orally. The combination of hydroxylpropyl-β-cyclodextrin (HPβCD) with angiotensin-(1–7) (HPβCD/angiotensin-(1–7)) protects angiotensin-(1–7) from enzymatic degradation allowing angiotensin-(1–7) to be administered orally [28]. Also, AVE 0991 was the first nonpeptide angiotensin-(1-7) receptor agonist developed with the intention of stimulating the Mas receptor. This compound mimics the Ang-(1–7) effects in several organs such as vessels [29,30], heart [31] and kidney [32,33].

Also, it has been recently proven that liraglutide, a potent agonist of the GLP-1 receptor, is able to potently modulate the pulmonary expression levels of the RAS components including ACE and ACE2, in adult rats [24]. Liraglutide also increased endothelial nitric oxide synthase (eNOS). It also promoted the positive effects of ACE2-Ang(1–7)-MasR in restoring lung function, so we rely on this drug to counteract some fatal effects of COVID-19 as a symptomatic indirect effect.

Conclusion

COVID-19 attaching with ACE2 might result in low activity of ACE2 and low level of Ang (1-7), which explains many different changes co-related with the COVID-19 infection. It seems the COVID-19 affect mainly the heart so the highest mortality rates are related to CVD. Interaction between COVID-19 and ACE2 receptor induce high increase in Ang II and low Ang-(1-7), so neutralizing these effects will give the immune system the time and ability to kill the virus and decrease the other fatal diseases induced by the decrease in Ang-(1-7). A suggestion of using of Ang-(1-7) and/or GLP-1 receptor agonists might have a high benefit role in the symptomatic treatment of COVID-19, as they control the main side effects of virus induced disease, and inflammatory mediators.

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