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Short communication

Apelin-potential therapy for COVID-19?

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ABSTRACT

We believe that, in parallel to the attempts for direct blockade of the SARS-CoV-2 penetration into host cell and repurposing drugs, finding new therapeutic strategies for patients with lung injury or cardiovascular complications/coagulopathies associated with COVID-19 should be paid particular attention. Apelin or its receptor agonists are of great potential treatment for COVID-19 through suppressing angiotensin-converting enzyme (ACE) and angiotensin II (Ang-II) production, as well as, down-regulating angiotensin receptor 1 (AT1R) and ACE2 up-regulation. These drugs have potential to improve acute lung injury and cardiovascular/coagulopathy complications in COVID-19 which are associated with elevated Ang-II/Ang(1–7) ratio.

1. Introduction

Since December 2019, the novel coronavirus (SARS-CoV-2) was identified in the pneumonia cases of unknown etiology in Wuhan, China, and is rapidly spreading around the world. Given the rapid spread and strong transmissibility of SARS-CoV-2, the epidemiologic picture is varying on a daily basis. The respiratory symptoms including acute respiratory distress syndrome (ARDS) has been recognized as the major cause of death in the patients infected with SARS-CoV-2, and the mortality remains very high despite the different therapeutic regimens including repurposed antivirals, anti-inflammatory agents, and immunomodulators. Scientific evidence is lacking in many domains as Coronavirus disease 2019 (COVID-19) is a novel disease and comprehensive knowledge of pathophysiology remains incomplete. So far, drug repurposing and potential pharmaceutical treatments such as antiretroviral lopinavir-ritonavir, and antimalarial hydroxychloroquine and chloroquine, the drugs thought to be the prospects for treating Covid-19, failed to have any effect in the first trials, whereas may even raise the risk of mortality. Therefore, finding potential therapeutic targets for COVID-19 can be timely and of greatest importance to improve clinical outcome and reduce mortality.

The renin-angiotensin system (RAS) is a key mechanism underlying ARDS and cardiovascular diseases, so that the recent clinical findings from SARS-CoV-2-infected humans and previous studies of SARS-CoV spike protein-infected mice demonstrate the activation of the RAS and remarkable increased serum Ang-II have a linear correlation to worsening ARDS symptoms that was partly reversed by pharmacological inhibition of AT1R in the mice [1]. By contrast, angiotensin-converting

enzyme 2 (ACE2) cleaves Ang-II to Ang(1–7) and protects against SARS-CoV-triggered severe acute lung injury (ALI) and progression to ARDS. The viruses strongly bind ACE2 for host cell entry and down-regulate ACE2 expression that leads to excessive Ang-II formation and the subsequent ALI [1]. This might be the rationale for the ongoing clinical trials of recombinant human ACE2 (rhACE2) for coronavirus-associated ALI and the cardiovascular/coagulation complications [2]. Therefore, an appropriate therapeutic strategy for improving the lung injury and adverse cardiovascular outcome in COVID-19 could be the suppression of the RAS by simultaneous inhibiting Ang-II production and AT1R and activating ACE2.

2. SARS-CoV-2 and ACE2

ACE2 is a key counter-regulator of the RAS and has considerable homology to ACE that exhibits 42% sequence identity and 61% sequence similarity to ACE within the C-terminal domain [3]. Both ACE, the enzyme that converts Ang-I to Ang-II, and ACE2 are expressed and abundant in the human alveolar epithelial cells and extrapulmonary organs including the heart and endothelium. ACE2 also acts as the essential receptor for some respiratory viruses including SARS-CoV-2 and SARS-CoV, through which the viruses gain entry to host cells [1,4,5]. Binding of SARS-CoV-2 spike protein to ACE2 followed by the proteolytic cleavage of ACE2 by transmembrane serine protease 2 (TMPRSS2) leads to increased internalization and shedding of ACE2 from cell surface, and consequently decreased Ang(1–7)/Ang-II ratio [5]. Accordingly, down-regulation or severely impaired activity of ACE2, along with dominant increase in ACE activity and the subsequent Ang-II

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formation have been seen in patients with ARDS [1]. The elevated Ang-II binds its receptor AT1R that can cause severe adverse effects including (1) a rapid vasoconstriction and limited pulmonary circulation, leading to vascular permeability and pulmonary edema in hypoxic condition; (2) boost inflammatory responses; (3) enhanced reactive oxygen species (ROS) production, (4) accelerated apoptotic pathways, and (5) promoted pulmonary fibrotic events [6]. The excessive Ang-II promotes vascular inflammation through the enhancement of adhesion molecules, pro-inflammatory cytokines and chemokines which may also contribute to the hypercoagulable state and endothelial dysfunction. Moreover, activation of the RAS stimulates transcription factor NF- κ B which converts the normal anticoagulant endothelium into a procoagulant surface, expressing tissue factor (TF) with activated plasminogen activator inhibitor-1 (PAI-1) [7].

3. Apelin-APJ system

Apelin peptides are endogenous ligands of the G protein-coupled receptor APJ, which presents in vascular endothelial cells and, particularly, lung tissue. Apelin is a well characterized cardioprotective peptide in the late stages of heart failure, thereby exogenous administration of apelin can augment cardiac output and contractility in the failing hearts and consequently improve the cardiac performance [8]. Previous *in vitro* and *in vivo* studies have exhibited the apelin-APJ system counteracts the effects of ACE-Ang-II-AT1R axis and exogenous apelin negatively regulates the RAS. Given that the SARS-CoV-2 infection induces ACE2 down-regulation and consequently activation of ACE and Ang-II signaling, it is predictable that apelin has potential of alleviating the respiratory and cardiovascular complications through up-regulating ACE2, which itself enhances Ang(1–7)/Ang-II ratio and suppresses Ang-II signaling. On the other hand, ACE2 up-regulation may increase the risk for susceptibility to SARS-CoV-2 infection, therefore apelin or its analogues are proposed to be used in the late stages of COVID-19 when the viral load is reduced. Even though, the recent findings elucidate that ACE inhibitors and AT1R blockers, which were presumed to up-regulate ACE2, would not predispose to viral infection and severity of COVID-19, but were associated with significantly lower expression of ACE2 and the viral entry cofactor TMPRSS2 [9–11].

4. Apelin and COVID-19

The recent cohorts of COVID-19 patients confirm that hypertension and other cardiovascular diseases are comorbidities in almost one-third of the cases who developed ARDS [12]. Experimental and clinical studies suggest that Ang-II mediates inflammation systemically in the lung, heart, and vascular endothelial cells. Moreover, ACE2, the receptor for the SARS coronavirus, was identified as a regulator of acute lung injury, and heart failure [13]. Since SARS-CoV-2 binds and down-regulates ACE2 and consequently activates Ang-II-mediated pathological pathways in the endothelial and epithelial cells in the lung, heart and vasculature, apelin is assumed to play a critical role in alleviating Ang-II-mediated acute lung and cardiovascular injuries and prothrombotic events in COVID-19 patients. Although there is absence of basic and clinical evidence on therapeutic effects of apelin or its analogues on COVID-19 infection and the associated severe complications, preclinical studies to date demonstrate that these peptides are able to ameliorate the severity of ALI by reducing lung fluid accumulation, cytokine secretion, and hypoxemia, which occur in COVID-19-associated ARDS, and lead to downstream injury to the heart, kidney, and other organs [14]. Therefore, these peptides may potentially block acute effects of COVID-19, and their beneficial effects may extend to protecting other organs from the cytokine storm and reducing mortality.

The apelins-12 and -13 inhibit the vasoconstrictive effect of Ang-II and confers beneficial cardiovascular effects through ACE2/Ang(1–7)-and/or L-arginine/endothelial nitric oxide synthase (eNOS)/nitric oxide (NO)-dependent signaling pathways and prostacyclin (PGI₂)

activation [15]. Apelin protects against cardiac fibrosis and vascular remodeling through blocking Ang II-induced PAI-1 gene expression and increasing NO production [16]. Experimental studies on diabetic rats have demonstrated that apelin-13 ameliorates inflammation and oxidative stress through significant down-regulation of AT1R gene expression and conversely up-regulation of ACE2 gene expression in adipose tissue. Importantly, apelin-13 could confer a greater AT1R down-regulation when was co-administered with angiotensin receptor 1 blocker Losartan [17].

Apelin protects against ALI and ARDS through suppression of NF- κ B- and NLRP3 inflammasome-mediated inflammatory responses and secretion of IL-1 β and IL-18 from cells. Apelin also down-regulates mitochondrial ROS-triggered oxidative damage and mitochondria apoptosis [18]. Studies of animal models of ARDS have shown that post-injury activation of apelin-APJ system alleviates pulmonary inflammation and lung injury responses, and improves the oxygenation and lung edema by activating Akt-eNOS signal transduction and inhibiting the pro-inflammatory tumor necrosis factor- α (TNF- α), monocyte chemoattractant protein-1 (MCP-1) and oxidative stress. Deletion of apelin in the mice have been shown to induce the Ang-II-mediated pro-fibrotic processes, e.g. transforming growth-factor beta (TGF- β) and matrix metalloproteinase (MMPs) signaling, in the heart and lung, while exogenous apelin attenuated the TGF- β expression and further Ang-II-stimulated cardiac remodeling and pulmonary fibrosis [18]. ALI/ARDS is certainly associated with pulmonary endothelial injury and inflammatory/oxidative/procoagulant responses. Importantly, apelin expression is enhanced in response to ARDS and activation of apelin/APJ system protects against Ang-II-induced endothelial inflammation and prothrombotic event. Thus, apelin might have potential of anti-thrombotic effects by increasing Ang(1–7)/Ang-II ratio and blocking the Ang-II-AT1R binding (Fig. 1).

In addition to the therapeutic effects, apelin can potentially act as a predictor in the development of coagulopathies and cardiovascular disorders, including pulmonary embolism (PE) [18]. Apelin-13 has been reported to acutely enhance in the serum of patients with early-stage PE. Accordingly, apelin expression in lung tissue is up-regulated in a dog model of acute PE within the first hours and declined within 24 h, whereas intravenous administration of apelin reduces mean pulmonary arterial pressure and vascular resistance [18]. On the other hand, Ang-II elevation may cause the down-regulation of apelin and its receptor in the late stages of pathological status including hypoxia, which is a major manifestation of PE. Thus, exogenous apelin can possibly ameliorate the hypoxic state through inhibition of the excessive Ang-II generation in the later stages of SARS-CoV-2 infection. The potential therapeutic effect of apelin or its receptor agonists absorbs greater attention when the recent reports from different countries confirm the distinct abnormal coagulation parameters (e.g. prothrombin time, INR and activated partial thromboplastin time) and PE in hospitalized patients with severe COVID-19 disease [12,19]. Importantly, the COVID-19 non-survivors have shown increasingly high levels of thromboembolism predictive parameters, including D-dimer and fibrin degradation products (FDP), and cases of disseminated intravascular coagulation (DIC) [12].

5. Clinical potential in COVID-19

Extrapolating data from experimental and clinical implications of drugs targeting apelin/APJ system in pulmonary and cardiovascular pathologies to COVID-19 suggests that apelin or its receptor agonists up-regulate ACE2 or increase its activity, thereby leading to suppression of ACE-Ang-II system that drives acute lung injury, coagulopathies and acute/chronic cardiac injury in COVID-19 patients. Moreover, apelin could be a plasma marker for the lung and cardiac injuries. To date, a plethora of apelin receptor biased agonists have been characterized and MM07, among all, has the highest affinity to apelin receptor and efficacy to enhance cardiac output and vasodilation, as well as, to alleviate

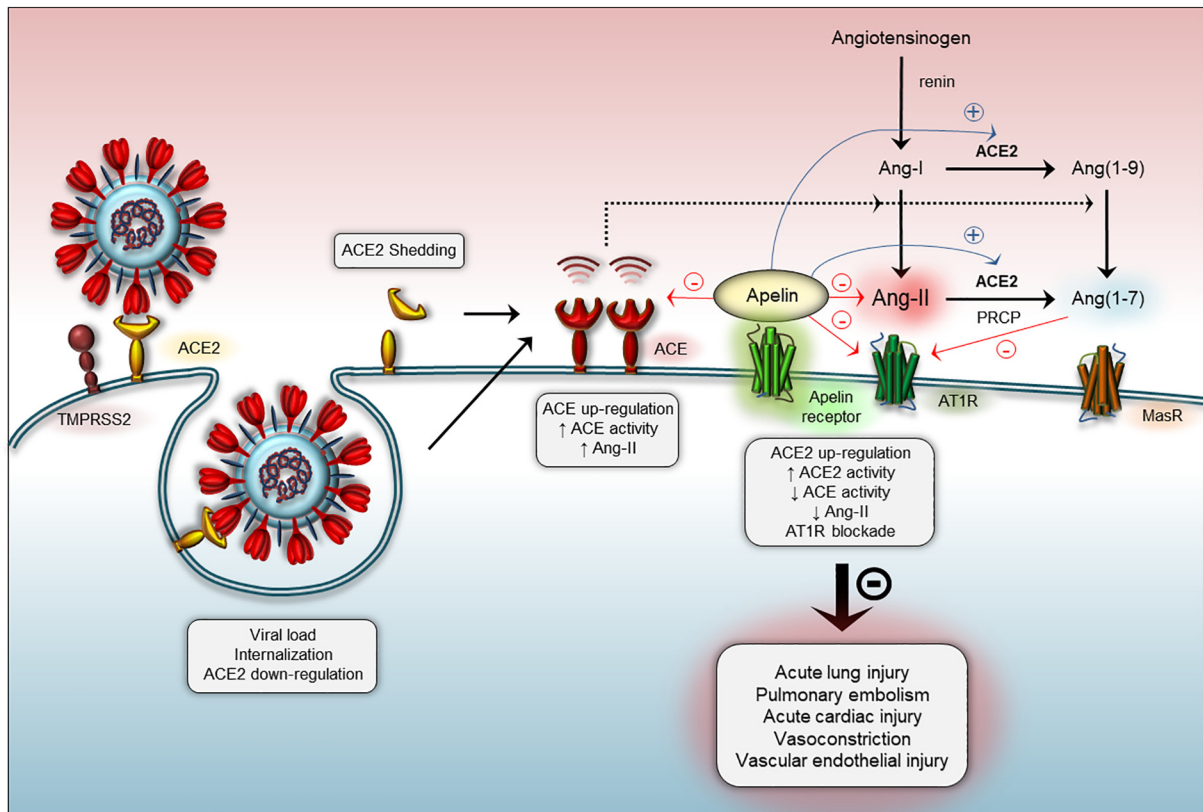


Fig. 1. The schematic of the hypothesis on the beneficial apelin-mediated down-regulation of renin-angiotensin system in COVID-19 disease.

pulmonary arterial hypertension and pulmonary vascular remodeling in humans and rats [20]. MM07 can ameliorate myocardial ischemia–reperfusion injury and ischemic cardiomyopathy certainly by suppressing mitochondrial ROS production, delaying the opening of mitochondrial permeability transition pores (mPTP) and lipid peroxidation [8]. Another endogenous apelin receptor agonist Elabela/Toddler activates the receptor downstream pathways, and induces aorta vasodilatation, more importantly, in response to Ang-II stimulation [15]. The small-molecule biased agonist CMF-019 potentially elicits a cardioprotective effect in heart failure and myocardial infarction, since this compound could increase cardiac contractility and cardiac output with limited effects on vasculature in rats with experimental left ventricle catheterisation and jugular vein cannulation [21]. Besides, the apelin receptor agonists are capable of negatively regulating ACE-Ang-II-AT1R axis through heterodimeric interaction of apelin receptor and AT1R, which modulates their protective effects in the cardiovascular and pulmonary tissues [8].

6. Conclusions

In conclusion, we believe that, in parallel to the intriguing attempts for direct blockade of the SARS-CoV-2 penetration, finding new therapeutic strategies for patients with ongoing lung injury or cardiovascular complications/coagulopathies associated with COVID-19 should be paid particular attention. Nevertheless, failure of the majority of the current results of the drug repurposing strategies for COVID-19 sounds alarm despite of the initial encouraging data. This warns us to cautiously propose new drugs and therapeutic regimens for patients with COVID-19 in the critical circumstance. Therefore, additional, experimental and clinical studies are urgently required.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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