SARS-CoV-2 – the hidden agonist of the pressor arm of renin-angiotensin system: considerations for statins and propionate derivatives.

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Abstract

Coronavirus disease 2019 (COVID-19) has become a serious healthcare problem, causing more than 2 million fatalities worldwide. Several treatments used for the management of chronic diseases such as hypertension, cardiovascular disease, diabetes and arthritis were shown to increase the expression of the receptor exploited by the virus, the angiotensin-converting enzyme 2 (ACE2), in vitro. This raises concerns on the safety of continuing such drugs or switching to other classes that don’t interfere with the receptor exploited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Here we emphasize the mechanisms behind the regulation of ACE2 expression by several widely used drugs with possible interactions with COVID-19. Moreover, we discuss how the physiological mechanisms of attenuating inflammation and fibrosis can lead to increased expression of the receptor exploited by the virus and how this expression is further influenced by statins, propionate derivative nonsteroidal antiinflammatory drugs (NSAIDs) and renin-angiotensin system (RAS) blockers.

Keywords: SARS-CoV-2, Renin-Angiotensin System, Statins
Introduction

In the context of the current pandemic with the SARS-CoV-2, several measures need to be taken to limit the fatality rates in the most vulnerable categories—elderly and people associating cardiovascular disease and diabetes [1].

SARS-CoV-2 exploits ACE2, a type I integral membrane protein mainly distributed in the lungs, for mediating its fusion with the human host cells, potentially causing severe acute respiratory syndrome (SARS) [2]. In acute lung injury, downregulation of ACE2 leads to dysregulation of renin-angiotensin system (RAS) with increases in vascular and capillary permeability and acute pulmonary edema. But the receptor is also distributed in the heart, kidney and endothelial cells [3]. This makes heart, kidney and endothelia the next organs with the highest viral burden after the lungs, leading to cardiac failure, arrhythmias, myocarditis, acute kidney injury, gastritis and liver dysfunction in severe cases.

RAS regulation through ACE2

ACE2 is an important component of the ACE2/Ang(1-7)/MasR and angiotensin receptor (AT₂R) depressor arm, accountable for counteracting vasoconstriction, proliferation, oxidative stress, fibrosis and pathogenesis of cardiovascular disease which are all effects of the ACE/AngII/AT₁R pressor arm of RAS [4]. This turns SARS-CoV-2 in a real antagonist of the depressor arm of RAS leading to exacerbated effects of the pressor axis. (Fig. 1). Blocking the ACE has no effect on ACE2 and might worsen the matters as it is also involved in the functioning of the depressor arm, turning Ang (1-9) into Ang (1-7) - the active compound that binds to the ACE2 in its normal functioning.

![Fig. 1. Blocking angiotensin-converting enzyme 2 (ACE2) as a result/because of SARS-CoV-2 infection](image-url)
The most important part of the renin-angiotensin system (RAS) is shown. In physiological conditions, angiotensinogen is secreted by the liver and is cleaved by an enzyme - renin, which is produced by the kidney, to angiotensin I (Ang I). Then, Ang I is divided into two directives. First Ang I is converted into angiotensin II (Ang II) (the active configuration of the hormone) by an enzyme produced in the lungs – angiotensin-converting enzyme (ACE). Ang II through AT1 receptor thus leads to increased vasoconstriction, inflammation, atrophy, and fibrosis. ACE2 is an important component that inactivates Ang I by hydrolyzing Ang II to Ang (1-7), which together with MasR acts like a depressor arm and protective by promoting vasodilatation, hypotension, and apoptosis, similar to the AT2 receptor. Instead, in COVID-19 disease, the SARS-CoV-2 virus block ACE2, thus leading to RAS imbalance by inhibiting antagonist actions on Ang I.

While AT1R blockers (ARBs) could be better options for reducing the exacerbated effects of the pressor arm, they were shown to increase ACE2 expression in kidneys and heart [5,6]. Advice on not abstaining from ACE inhibitors or other RAS blockers in COVID-19 as there is insufficient clinical data in this regard, is being extensively debated [7,8].

**Effects of Statins and NSAIDs on ACE2 regulation**

Statins, which are widely used to lower cholesterol, and propionate derivatives, a distinct class of NSAIDs, can also regulate ACE2 expression. Statins are used in primary and secondary prevention of cardiovascular disease [9,10]. In the last decades their use has increased substantially across US and Europe [11] and as a result, an important reduction in cardiovascular mortality has been observed [12,13].

The effects of rosuvastatin on ACE2 were investigated in a murin model of vascular balloon injury. Here, a significant decrease in the expression of AT1 and levels of Ang II and P-ERK with a significant increase in the expression of ACE2 mRNA and protein, and levels of Ang (1-7) was observed in the statin treatment arm. This correlated with reduced hyperplasia from damage induced by balloon injury (intimal thickening by neoformation) as compared to the non-statin group [14]. This suggests that rosuvastatin mediates a less severe inflammatory response with reduced tissue pathology through the counteracting arm of the RAS.

Apart from reducing cholesterol, statins were previously shown to exert antiinflammatory and immunomodulatory effects [15,16]. Together with ARBs, statins have been involved in the reduction of oxidative stress [17], and endothelial dysfunction [18], being used to treat patients with sepsis, Ebola, Influenza virus and ARDS with encouraging results. A recent meta-analysis has assessed the effects of statins in patients with COVID-19, suggesting a reduction in fatal or severe disease by 30% [19]. This suggests an important implication in treating the host’s response rather than targeting the pathogen itself. In this regard, virologists stress out that a more important factor for the host’s
survival is the host’s response towards the pathogen rather than the viral load [20]. However neither of the previous viruses involved the overexpression of the viruses binding receptor as an effect of the treatment or physiological response to the pathogen. This is an important quality of ACE2 exploiting viruses such as SARS-CoV and the new SARS-CoV-2, as they seem to have adapted to such host responses of counteracting the pressor arm of RAS by mimicking a “Larnean Hydra” type of a reaction, through increases in ACE2 expression – its binding receptor.

A similar effect was seen with Ibuprofen, a propionate derivative, in reducing the ACE/Ang II/AT1R axis and enhancing the ACE2/Ang(1-7)/MasR and AT2R axis leading to an increased expression of the ACE2 for attenuating cardiac fibrosis in mice [21]. Propionate was shown to induce rapid intracellular acidification [22], a requirement for the autophagy machinery exploited by many RNA and most enveloped viruses, including coronaviruses, for their entry and replication [23-25]. The implications of propionic acid derivatives in COVID-19 are even more compelling as they are oxidizing agents. This effect can add to the already oxidizing effect of the viral infection which can lead to hemolytic anemia in G6PD deficient patients [26]. Since G6PD deficiency is not a rare occurrence and might go unnoticed in the absence of triggers, such associations could prove unfavorable for many asymptomatic carriers of the mutation affected by the pandemic which use propionate derivatives. A retrospective cohort study of 403 patients with COVID-19 found no differences in mortality rates or the need for respiratory support among patients using ibuprofen [27].

Although propionate inhibits cholesterol synthesis in the liver in a lesser extent [28], the most exploited property of propionate derivatives (ibuprofen, ketoprofen, naproxen, flurbiprofen, flunoxaprofen and carprofen) is the antiinflammatory and analgesic effect [29]. Statins and NSAIDs may influence the human body’s response to the infection and not the virus itself [20]. Both drugs can upregulate the activity of ACE2 and tissue receptors for ACE2 [30-32]. The debate on drugs which increase ACE2 expression in COVID-19 has also been addressed in the case of RAS blockers and there were no arguments to support changes in their current use [7,33].

One very large-cohort (8.3 million people) based analysis regarding ACE inhibitors and ARBs use in COVID-19 patients has found overall a reduced risk of the disease in these users. However, it indicated ethnic-specific effects of ARBs and ACE inhibitors with higher risk for COVID-19 [34]. A study of more than 800 thousand patients with hypertension has found that the use of ACE inhibitors and ARBs was not associated with a higher risk of COVID-19 while no antihypertensive medication was associated with increased risk of COVID-19 [35]. In a meta-analysis which focused on the use of ARBs in COVID-19 it appeared that ARBs are safe in the context of SARS-CoV-2
infection and should be continued [36]. Another meta-analysis indicated that patients receiving statins after COVID-19 diagnosis were at lower risk of mortality relative to non-statin patients [37]. A lower disease severity was also reported in COVID-19 patients receiving statins [38]. However, several authors highlight that the data on the interactions of ACE inhibitors and ARBS in humans in the context of SARS-CoV-2 infections are too limited to support or refute the assumptions and concerns regarding their influences on viral replication or disease outcome [39,40].

**Conclusions**

Whether increasing ACE2 receptor expression is detrimental due to increased number of receptors for viral fusion, or may actually be protective due to counteracting the effects of the exacerbated pressor arm of the RAS while reducing inflammation, remains to be further elucidated in SARS-CoV-2 infection.

From a mechanistic point of view, once the infection has already been established and spread in tissues, counteracting the pressor arm of RAS most likely becomes more beneficial than inhibiting viral entry since dysregulation of the RAS in the vulnerable population may indirectly prove more lethal than the direct effects of the infection itself on tissues. Whether the increased fatality in elderly and patients with cardiovascular pathologies and diabetes is due to exacerbation of the pressor arm of RAS or from iatrogenic induced ACE2 overexpression, or whether the ACE2 overexpression is the result of the protective mechanism against high inflammation, hyperplasia and fibrosis regulated through the depressor arm of RAS, or whether there is a vicious circle with this antiinflammatory pathway actually increasing the expression of the viruses binding receptor, remains elusive and raises more questions than answers.

Although switching to classes of blood pressure medications, lipid lowering drugs and NSAIDs that do not interfere with the RAS regulation and ACE2 expression may seem an option to be considered, there are no arguments at the current moment to support a detrimental effect of the use of statins or propionate drugs in COVID-19 patients. Destabilizing blood pressure with treatment changes is not a rare occurrence and would be an audacious move in infected patients and simply interrupting chronic medication is not an option and should be ruled out.

**Abbreviations:**

ACE2 – Angiotensin-Converting Enzyme 2  
ARB – Angiotensin Receptor Blocker  
ARDS – Acute Respiratory Distress Syndrome  
ATR – Angiotensin Receptor
COVID-19 – Coronavirus Disease 2019
NSAIDs – Nonsteroidal Antiinflammatory Drugs
RAS – Renin-Angiotensin System
SARS-CoV-2 – Severe Acute respiratory Syndrome Coronavirus 2

Statements:

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