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feature



Drugs acting on the renin–angiotensin system and SARS-CoV-2

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the ongoing global Coronavirus 2019 (COVID-19) pandemic, resulting in thousands of deaths worldwide and representing a health challenge with few precedents in human history. Angiotensin-converting enzyme 2 (ACE-2) facilitates the access of SARS-CoV-2 to cells. Therapeutic agents acting on the renin–angiotensin system (RAS) might be able to modulate the concentration of ACE-2 and the various components of the system. Here, we discuss current pharmacological, molecular, and clinical evidence to investigate whether drugs acting on RAS with modulation of the ACE-2 concentration have added value in combating SARS-CoV-2 infection. We also highlight the possible deleterious action of the ACE/Ang-II/AT-1r axis and possible beneficial role of the ACE-2/Ang 1-7/MasR axis in acute respiratory distress syndrome (ARDS) caused by SARS-CoV-2, discussing the possibility of addressing the various RAS components with drug treatments to improve clinical outcomes.

SARS-CoV-2

SARS-CoV-2 is responsible for the current global COVID-19 pandemic, causing thousands of deaths and for a health challenge with few precedents in human history. SARS-CoV-2 is a family of RNA viruses capable of infecting humans and causing respiratory tract infections, respiratory distress syndrome, and serious lung injury in some cases [1]. SARS-CoV-2 has an ~80% genome similarity to that of SARS-CoV responsible for a 2003 outbreak [2,3]. SARS-CoV-2 infection occurs in three stages: (i) asymptomatic or mildly symptomatic; (ii) moderately severe, characterized by a pulmonary inflammation; and (iii) very severe, characterized by a generalised inflammatory state affecting all tissues causing multiorgan

dysfunction [4]. Biochemical interaction studies have shown that SARS-CoV-2 enters host cells mainly through the use of the spike protein (S) [5]. This protein contains two functional subunits S1 and S2: S1 binds the surface receptors of the host cells, whereas S2 is responsible for membrane fusion between the virus and the host cell [6]. SARS-CoV-2 penetrates cells using the S protein via the ACE-2 receptor on the cell surface, which is widely present in epithelial cells of the respiratory mucosa [6]. ACE-2 is also a converting enzyme that is part of RAS. It is unclear whether an increase in ACE-2 is responsible for a greater likelihood of COVID-19 infection. The level of expression of ACE-2 in the respiratory tract of smokers is higher than that of nonsmokers and SARS-CoV-2 is more

likely to infect smokers [7]. Lung tissues are probably an easier entry route for SARS-CoV-2 because 83% of ACE-2 receptors are present in type-II pneumocytes that produce surfactants that prevent alveoli from collapsing [8]. In addition, the expression of ACE-2 changes during the various stages of the infection. To date, there is no conclusive evidence on the role of RAS and ACE-2 in the three stages of SARS-CoV-2 infection. Drugs acting on RAS are widely used in the treatment of cardiovascular diseases, but what is the correlation between these drugs, RAS, and COVID-19? Could they have a protective role by modulating the expression of RAS components or should they be considered risk factors for COVID-19?

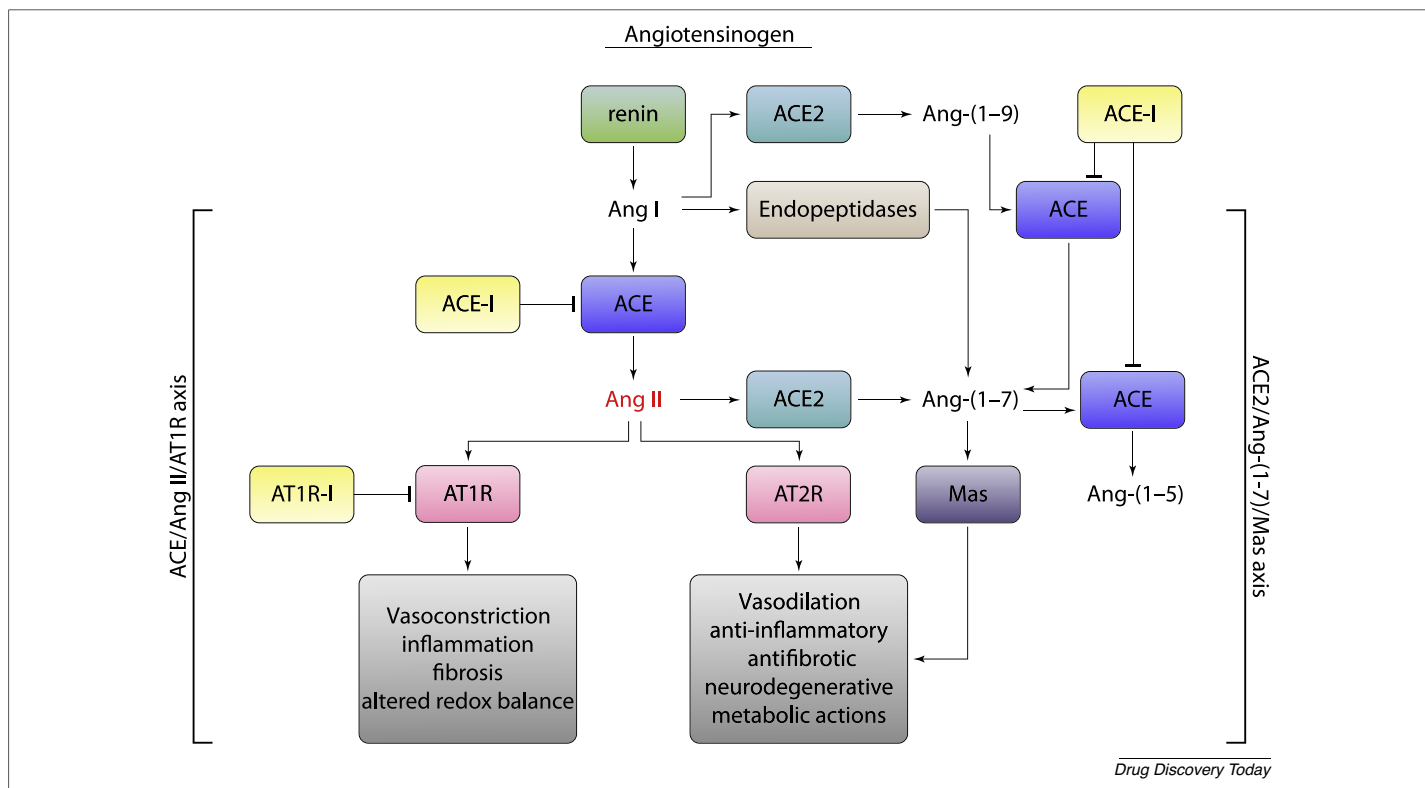


FIGURE 1

The renin–angiotensin system (RAS). Vasodilatory, anti-inflammatory, and antifibrotic effects mediated by stimulation of the AT₂ (AT₂R) and Mas receptors (MasR) could be of clinical benefit during the most severe stages of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, whereas the vasoconstrictory, proinflammatory, and profibrotic effects mediated by stimulation of AT₁-r could increase lung damage.

RAS and SARS-CoV-2

RAS is a physiological system controlling blood pressure and electrolyte balance in the body. It also exerts numerous local effects aimed at regulating tissue physiology and homeostasis [9]. RAS can influence growth, proliferation, differentiation, and cell apoptosis, and also has effects on inflammation. RAS alterations are involved in many diseases, including atherosclerosis, diabetes mellitus, and viral infections, such as SARS-CoV-2 [10,11]. Therefore, it is crucial to investigate how the expression of the various components of RAS vary in tissues during SARS-CoV-2 infection and whether a change in their expression caused by drugs acting on RAS could have repercussions and correlations with COVID-19 infection at various stages.

The classical route of RAS includes subsequent enzymatic reactions that lead to the conversion of the angiotensinogen substrate (AGT) into the active angiotensin-II (Ang-II) peptide, which binds to its specific membrane AT receptors to exert its effects. In the bloodstream, AGT is converted to angiotensin I (Ang-I) by renin; Ang-I is further processed by angiotensin-converting enzyme (ACE) to release

vasoactive angiotensin-II (Ang-II). In addition to Ang-II production, ACE can degrade several vasodilator peptides, including bradykinin and kallikrein [12]. Bradykinin causes vasodilation through the production of prostaglandins and nitric oxide (NO) and inhibits the proliferation of smooth vascular muscle.

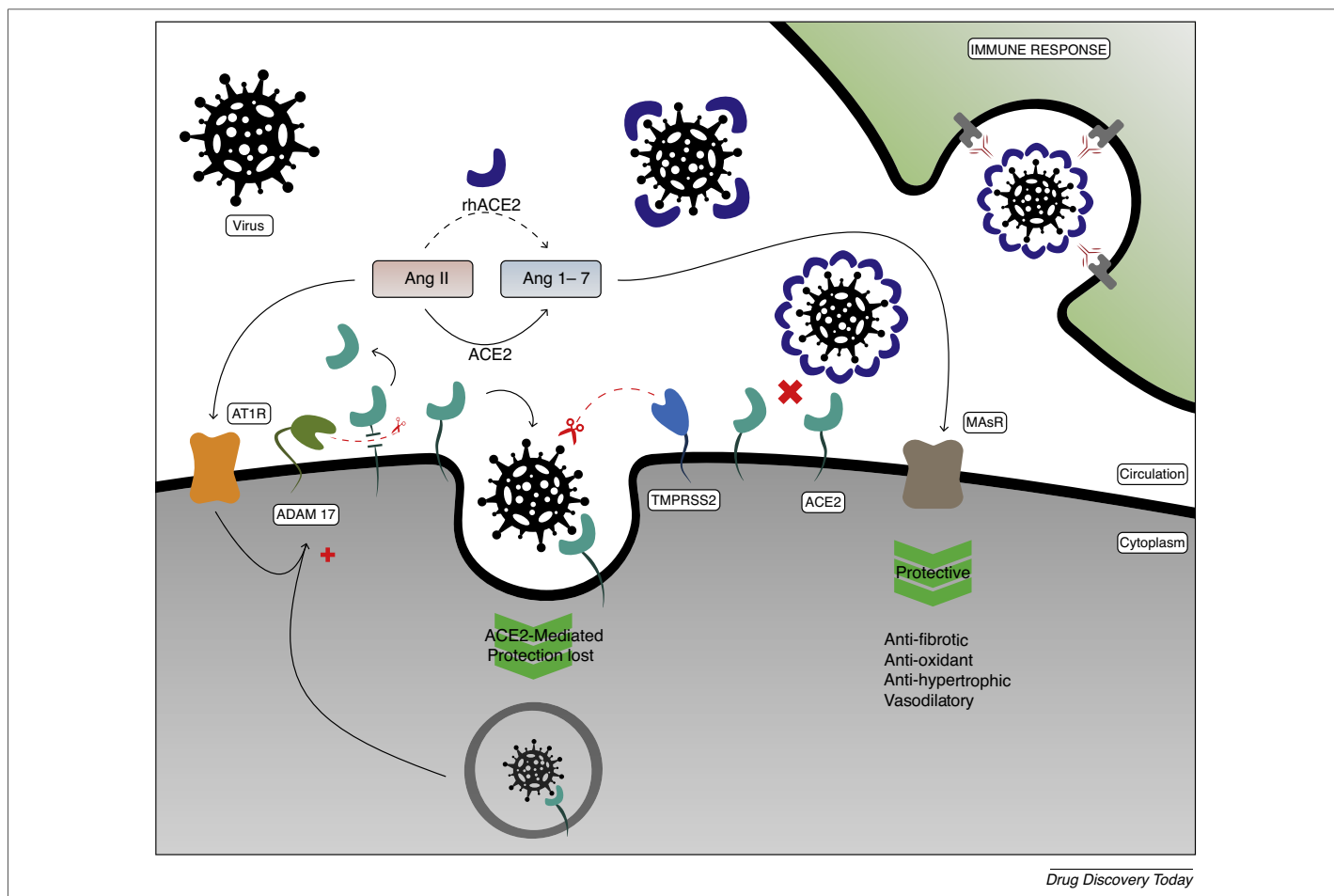
Ang-II acts on receptors to regulate blood pressure and electrolyte balance. At the cellular level, Ang-II modulates cell contraction, growth, differentiation, and apoptosis; it can also promote the production of other cytokines, the expression of adhesion molecules and subsequent recovery of inflammatory cells, chemotaxis, and macrophage activation. The increase in Ang-II formation induces inflammation and Ang-II is itself a powerful proinflammatory cytokine as well as a growth factor. It also activates the transcriptional factor nuclear factor (NF)-κB, a key factor of nuclear transcription in inflammatory and fibrotic diseases, and its activation allows the transcription of several inflammatory genes, including *IL6* and *IL1*, which are responsible for the cytokinic cascade and the hyperactive inflammatory state that is generated mainly during the third stage of COVID infection [13,14].

Nonclassical RAS pathways include angiotensin 1-7 (Ang 1-7) from Ang-II and angiotensin 1-9 (Ang 1-9) from Ang-I by ACE-2 conversion. Ang 1-7 oppose the actions of the AT₁ receptor (AT-1 r) mediated by Ang-II [15] and this leads to vasodilator/antiproliferative effects. ACE-2 can generate Ang 1-7 directly from Ang-II, or indirectly from Ang-I via Ang 1-9 intermediates [16]. Ang 1-7 exert their effects via the Mas receptor (MasR). By binding to MasR, Ang 1-7 can induce vasodilation, cell growth inhibition, antithrombosis, antifibrosis and anti-inflammatory effects [17].

Ang 1-9 exert several effects *in vivo* and *in vitro* independently of Ang 1-7-mediated MasR activation, possibly through AT₂ receptors (AT₂-r). Ang 1-9 also have antifibrotic and antiproliferative effects [18] (Fig. 1).

Roles of ACE-2, Ang 1-7, and Ang 1-9

SARS-CoV-2 penetrates cells by binding S protein to ACE-2 (Fig. 2) [19]. In the current SARS-CoV-2 pandemic, evidence shows that ACE-2 receptors are the gateway to the virus. ACE-2 converts Ang-II to Ang 1-7, and converts Ang-I to Ang 1-9, which in turn is converted to Ang 1-7 by ACE and neprilysin. ACE-2 receptors



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FIGURE 2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) penetrates cells by binding of the peak viral protein (spike; S) to angiotensin-converting enzyme 2 (ACE-2). ACE-2 converts angiotensin (Ang)-II to Ang 1-7. The latter have opposite biological actions to Ang-II (i.e., antifibrotic, antioxidant, and antihypertrophic effects) through stimulation of Mas receptor (MasR).

are expressed in the heart, vessels, intestine and lungs [20,21]. ACE-2 occurs mainly on cell membranes and there is very little in circulation in soluble form.

The role of ACE-2 in the pathophysiology of SARS-CoV-2 infection is not yet fully understood, because ACE-2 is not only the virus entry receptor, the modulation and variation of RAS and ACE-2 during the various stages of infection have been demonstrated, and the role of ACE-2 in infected lung tissue is unclear, especially during the more severe stages of infection, where it appears to have a protective role. These new findings could have a major impact on the development of new effective therapies to combat SARS-CoV-2 infection, or suggest additional therapeutic solutions for drugs modulating the RAS system.

To prevent viral replication, an interesting line of research could be that of the use of anti-ACE-2 antibodies to block the binding of SARS-CoV-2 to the receptor, whereas another option could be to block upstream the enzymatic cascade of

RAS and decrease the expression of ACE-2 [8]. During the more severe stages of SARS-CoV-2 infection, where ACE-2 could have a protective role, an increase in ACE-2 expression could be beneficial. Other important aspects to consider are that the biological effects of Ang-II are vasoconstrictive and stimulate the release of aldosterone, which, in high concentrations, can also cause myocardial hypertrophy, interstitial fibrosis, endothelial dysfunction, and increased inflammation, oxidative stress, and coagulation, biological effects that, if altered, can cause serious complications in patients with COVID-19 [22,23].

Finally, Ang-II can cause increased inflammation through production of IL-6, tumor necrosis factor (TNF)- α and other inflammatory cytokines [24–26]. However, all these biological effects are mediated by AT-1 receptors. By contrast, ACE-2 can reduce the negative effects of Ang-II through several mechanisms, such as degradation of Ang-II and Ang 1-7 formation. As described earlier, recent evidence showed that Ang 1-7 can also be

formed by the action of neprilysin. Ang 1-7 has opposite biological effects to Ang-II through MasR and AT2-r. MasRs are expressed on the surface of the smooth muscle cells of the bronchial muscle and alveolar epithelium [27,28], where Ang 1-7 exerts anti-inflammatory and antifibrosis effects [29,30]. In addition, MasR are expressed on platelets, where Ang 1-7 mediates antiaggregant effects [31–33] by increasing prostacyclin and NO release [34]. Studies have demonstrated an anti-hypertrophic role for the Ang (1-9) receptors independent of Ang 1-7 MasR [35], proactively mediated by the AT2 receptor (AT2R) [8].

Agents acting on RAS and effects on ACE-2, Ang-II, Ang 1-7, and Ang 1-9

Based on the earlier considerations, the crucial role of RAS and ACE-2 in acute respiratory distress syndrome (ARDS) caused by SARS-CoV-2, and the correlation with the inflammatory status of lung tissues during the more severe stages of COVID-19 infection, RAS-modulating therapeutic agents could indirectly have

TABLE 1

Agents active against RAS that modulate ACE-2 and their hypothetical use in the various stages of SARS-CoV-2 infection^a

Phase of infection	ACE-2 (-)	ACE-2 (+)
1	DRIs	
2		ACEis
3		ARBs

^a During the prevention and Phase 1 stages of viral infection, it might be useful to decrease ACE-2 concentrations with DRIs, whereas, during the more severe stages, an increase in ACE-2 with ACEis and ARBs might have a protective role.

an important role in treating SARS-CoV-2 viral infection. Agents that are active against RAS interfere with various stages of the system, such as ACE inhibitors (ACEis), which block the AT-1 receptors of Ang-II (ARBs), or by directly inhibiting renin (renin inhibitors; DRIs) [36]. These therapeutic agents are indicated for the treatment of cardiovascular diseases, such as hypertension and ischemic heart disease. Acting at different levels of the system, drugs acting on RAS can cause heterogeneous effects on the modulation of peptides and enzymes involved in the cascade. *In vitro* and animal studies have shown that the use of ACEis increases the levels of ACE-2, while the use of ARBs causes an increase in the expression and activity levels of ACE and ACE-2, [37,38]. Finally, administration of DRIs is associated with a reduction in the expression of ACE and ACE-2 [39,40] (Table 1).

An increase in ACE-2 concentrations has already been documented in both mouse models and patients treated with ACEis and ARBs. An increase in the level of expression of these viral receptor suggest an increase in the infectious power SARS-CoV-2. During phase 1 of the infection, the virus penetrates the cell and replicates; thus, during this phase it might be useful to administer a DRI that, by acting upstream [41], lowers concentrations of ACE and ACE-2, decreasing the concentration of receptor proteins for the virus to attach to. Conversely, during phase 2 or 3 of the disease, where there is an overactive inflammatory state and where ACE-2 appears to have a protective role particularly in the respiratory tract [42], it might be appropriate to increase ACE-2 with ACEis or block the inflammatory effects of Ang-II using ARBs, which also increase the expression of ACE-2 itself. Other aspects to consider are that the use of ACEis could lead to an increase in bradykinin by decreasing ACE metabolism [43] and activating the inflammatory system.

Moreover, the use of ARBs could bring further benefits, in that blocking the AT-1 receptor would cause greater activation of AT2R by Ang-II, with resulting anti-inflammatory and antifibrosis effects. Thus, the use of ARBs might have

added value compared with ACEis [44,45]. Finally, an increase in ACE or ACE-2 could lead to increased degradation of bradykinin, avoiding pro-inflammatory effects. In addition, for these three classes of drug acting on RAS, there is a potential indirect protection against SARS-CoV-2. Patients with cardiovascular disease are at high risk of pneumonia and studies have shown that the use of RAS-blocking drugs decreases this risk [46,47].

Epidemiological evidence

As described earlier, *in vitro* and animal studies have shown that RAS-modulating agents can modify polypeptides and enzymes in the system; in particular, ACEis and ARBs can increase the expression of ACE-2. However, current epidemiological evidence is at odds with expected results based on *in vitro* and animal evidence. Mehra *et al.* [47] conducted a study with 8910 patients, and neither ACEis or ARBs were associated with an increased risk of infection or complications from COVID-19. Mancina *et al.* [48] conducted a case-control study of patients with COVID-19 in Italy and also showed no correlation between ACEi and ARB intake and increased risk of infection or COVID-19 complications. In addition, Reynolds *et al.* [49] conducted a study on 12 594 patients and showed no positive association between COVID-19 symptoms and ACEi and ARB use. Other epidemiological studies have reached similar conclusions [50,51].

Despite each of these studies having its own weaknesses, they all suggest that the continued use of ACEis and ARBs is not harmful in patients with Covid-19, and does not increase the likelihood of infection. Ultimately, more studies will be needed to clarify whether ACEis or ARBs are harmful to patients with COVID-19.

Discussion

During the current COVID-19 pandemic, concerns have emerged over the use of different classes of drugs and treatments [52], particularly whether drugs that modulate RAS increase the risk of infection and complications associated with SARS-CoV-2, or whether, by modulating the components of RAS, they are indirectly useful? It is

currently recommended not to discontinue treatment in patients with heart failure, chronic kidney disease, hypertension and associated diseases [53,54]. Therefore, there is currently no evidence to support the notion that the use of ACEis, ARBs, or DRIs could increase SARS-CoV-2 infectivity. By discontinuing therapy with RAS blockers, patients will experience a significantly increased risk of cardiovascular morbidity and mortality considering the proven benefit of the therapy [55]. In addition, there is evidence showing that the activation of the Ang-II/AT1 r axis promotes lung injury and is harmful, whereas an increase in the ACE-2/Ang 1–7/MasR axis protects against lung injury. For the latter, there is the potential to protect lung injury by increasing ACE-2 using recombinant ACE-2 soluble in humans (rhACE-2) in patients with COVID-19 (Clinicaltrials.gov #NCT04287686).

The discrepancy between *in vitro* and animal results and clinical epidemiological data can be explained in terms of the selective variation in ACE and ACE-2 in tissues during treatment with RAS blockers, because no studies on the effects of RAS blockers on the activity of ACE-2 in tissues in the upper or lower respiratory tract have been reported [56]. However, we believe that reducing ACE2 expression with DRIs either preventively or during phase 1 of viral infection could be an interesting option in the context of SARS-CoV-2 infection, and requires further investigation [57]. Although the clinical benefit of these pharmacological approaches has yet to be demonstrated, there is ample evidence to suggest that treatment with RAS blockers should not be discontinued in patients with COVID-19.

Declaration of interests

The authors declare no conflict of interest.

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