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Original article

Renin-angiotensin-aldosterone system and COVID-19 infection

Système rénine-angiotensine-aldostérone et infection à COVID-19

Joachim Alexandre [a,*], Jean-Luc Cracowski [b], Vincent Richard [c], Béatrice Bouhanick [d], 'Drugs, COVID-19' working group of the French Society of Pharmacology, Therapeutics

[a] *Service de pharmacologie, université de Caen-Normandie, UNICAEN, CHU de Caen-Normandie, EA 4650, 14000 Caen, France*
[b] *Université de Grenoble-Alpes, centre régional de pharmacovigilance de Grenoble, INSERM, HP2, 38000 Grenoble, France*
[c] *Service de pharmacologie, université de Rouen-Normandie, UNIROUEN, CHU de Rouen-Normandie, UMR Inserm U1096 EnVI, 76000 Rouen, France*
[d] *Service d'hypertension artérielle et thérapeutique PCVM, CHU de Rangueil, UMR 1027 université Toulouse 3, 1, avenue J.-Poulhes 31059 Toulouse cedex 9, France*

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ABSTRACT

With the multiplication of COVID-19 severe acute respiratory syndrome cases due to SARS-COV2, some concerns about angiotensin-converting enzyme 1 (ACE1) inhibitors (ACEi) and angiotensin II type 1 receptor blockers (ARB) have emerged. Since the ACE2 (angiotensin-converting enzyme 2) enzyme is the receptor that allows SARS COV2 entry into cells, the fear was that pre-existing treatment with ACEi or ARB might increase the risk of developing severe or fatal severe acute respiratory syndrome in case of COVID-19 infection. The present article discusses these concerns. ACE2 is a membrane-bound enzyme (carboxypeptidase) that contributes to the inactivation of angiotensin II and therefore physiologically counters angiotensin II effects. ACEis do not inhibit ACE2. Although ARBs have been shown to up-regulate ACE2 tissue expression in experimental animals, evidence was not always consistent in human studies. Moreover, to date there is no evidence that ACEi or ARB administration facilitates SARS-COV2 cell entry by increasing ACE2 tissue expression in either animal or human studies. Finally, some studies support the hypothesis that elevated ACE2 membrane expression and tissue activity by administration of ARB and/or infusion of soluble ACE2 could confer protective properties against inflammatory tissue damage in COVID-19 infection. In summary, based on the currently available evidence and as advocated by many medical societies, ACEi or ARB should not be discontinued because of concerns with COVID-19 infection, except when the hemodynamic situation is precarious and case-by-case adjustment is required.

Mots clés :
COVID-19
Système rénine-angiotensine-aldostérone
Hypertension artérielle

RÉSUMÉ

Avec la multiplication des cas de syndrome respiratoire aigu sévère COVID-19 dus au SRAS-COV2, certaines préoccupations concernant les inhibiteurs de l'enzyme de conversion de l'angiotensine 1 (IEC) et les antagonistes des récepteurs de type 1 à l'angiotensine II (ARB) ont été soulevées. L'enzyme membranaire ACE2 (enzyme de conversion de l'angiotensine 2) sert de récepteur au SRAS-COV2, permettant ainsi son entrée dans les cellules. Ainsi, la crainte qu'un traitement pré-existant par IEC ou ARB pourrait augmenter le risque de développer un syndrome respiratoire aigu sévère en cas d'infection au COVID-19 a émergé. L'ACE2 est une enzyme (carboxypeptidase) qui contribue à l'inactivation de l'angiotensine II et, par conséquent, s'oppose physiologiquement aux effets de l'angiotensine II. Les IEC n'inhibent pas l'ACE2. Bien qu'il ait été démontré in vitro que les ARB régulent positivement l'expression membranaire/l'activité tissulaire de l'ACE2, les études chez l'Homme ne sont pas concordantes. De plus, à ce jour, il n'y a pas de données pour soutenir l'hypothèse qu'un traitement par IEC ou ARB pourrait faciliter l'entrée cellulaire du SRAS-COV2 en augmentant l'expression membranaire et l'activité tissulaire d'ACE2. Enfin, certaines études soutiennent l'hypothèse selon laquelle l'augmentation de l'expression membranaire d'ACE2, l'administration d'ARB ou l'administration d'ACE 2 soluble circulante pourrait conférer des effets

* Corresponding author at: Service de pharmacologie, CHU de Caen, EA 4650, avenue de la Côte-de-Nacre, 14000 Caen, France.
E-mail address: alexandre-j@chu-caen.fr (J. Alexandre).

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protecteurs potentiels sur la survenue de lésions tissulaires inflammatoires sévères en cas d'infection par le COVID-19. Des essais thérapeutiques sont en cours. En résumé, sur la base des preuves actuellement disponibles et comme le préconisent de nombreuses sociétés savantes, les IEC ou ARB ne doivent pas être interrompus en raison d'une infection par le COVID-19 en dehors des situations où la situation hémodynamique est précaire avec alors un ajustement au cas par cas préconisé.

1. Introduction

Cardiovascular patients show increased risk of severe forms of coronavirus 2019 (COVID-19) infection [1,2]. Clinical manifestations are principally respiratory, but some patients may also show cardiovascular complications [1]. The present article reviews the current state of knowledge regarding the relation between the renin-angiotensin-aldosterone system (RAAS), particularly ACE2, and COVID-19, and between RAAS blockers and COVID-19.

2. ACE2 and COVID-19

In human physiology, peptides are degraded by a limited number of non-specific extracellular enzymes known as peptidases or proteases. These are membrane proteins, the active sites of which face the extracellular space. Endopeptidases cut within the peptide chain, while exopeptidases release C- or N-terminal amino acids. Angiotensin-converting enzymes are exopeptidases (carboxypeptidases), relatively specific to the amino acids surrounding the cut site, although these may be common to several peptides. It is therefore important to be aware that a given peptidase is not as such specific to a given peptide. Angiotensin-converting enzyme 2 (ACE2) is an enzyme (carboxypeptidase) mainly located in the membrane, circulating forms being created by enzyme splicing of the membrane anchor; it is homologous to the angiotensin-converting enzyme (formerly simply known as ACE but now better denoted ACE1) first described in 2000 [3,4]. ACE2 down-regulates the renin-angiotensin system and acts as a deactivator of angiotensin II (also known as angiotensin-(1-8), an active peptide causing vasoconstriction, pro-fibrosis, pro-inflammation action, stimulating aldosterone secretion by binding to the AT1 receptor), converting it into angiotensin-(1-7), an active peptide with opposite properties to angiotensin II [5]. Several animal studies showed that angiotensin-(1-7), by binding to the Mas receptor, induced vasodilatation and showed anti-fibrosis and anti-inflammatory properties [6] (Fig. 1). Angiotensin II is also deactivated by an aminopeptidase which converts angiotensin II into angiotensin III, which induces vasodilatation and increases natriuresis and bradykinin by preferential binding to AT2 receptors with 30-fold greater affinity than for AT1 receptors [7,8]. ACE2 also converts angiotensin 1 [also known as angiotensin-(1-10)] into angiotensin-(1-9), of unknown action, which is further converted into angiotensin-(1-7) by ACE1. The RAAS can thus be divided into an "activator" system comprising the classical and historical angiotensin II/ACE1/AT1R/aldosterone pathway, and an "inhibitor" system comprising the angiotensin-(1-7)/ACE2/MasR pathway, the latter able both to deactivate angiotensin II and counter its effects. The pharmacology of the angiotensin-(1-7)/ACE2/MasR pathway, in contrast to the angiotensin II/ACE1/AT1R/aldosterone pathway, has been little explored, but some in-vitro studies showed beneficial cardiovascular impact when activated, possibly involving GMPc-[8–12] elevation. ACE2 has also been reported to interact with the angiotensin-1 receptor AT1R, targeted by angiotensin II receptor blockers (ARB). ARBs counter AT1R-mediated effects of angiotensin II, thus stimulating angiotensin II liberation; in response to this increase in angiotensin II, they thus increase ACE2 expression [13]. ACE2 seems to be expressed by the cells of various organs, including heart, kidney, vessels, digestive tract, testicles, ENT region and lung [14–18].

To enter and infect cells, coronavirus have to recognise (via their spike surface glycoprotein) and to bind to a membrane receptor (protein, lipid carbohydrate) [19]. This depends on prior activation of the spike protein by human proteases including TMPRSS2 [20]. As a membrane enzyme with an extracellular domain, ACE2 seems to provide the entry into the human cells of SARS-COV2/COVID-19, and therefore acts as a receptor for this coronavirus [14,20] (Fig. 1). Precise identification of the SARS COV2 spike glycoproteins and their ACE2 binding site shows the latter to be identical to that of SARS COV [21], despite the two viruses being distinct and showing no more than 80% homology. Moreover, the affinity of SARS-COV2 for ACE2 is greater than that of SARS-COV [22,23]. This spike protein activation by TMPRSS2 proteases followed by SARS-COV2 binding to the extracellular domain of membrane ACE2 explains how the virus binds to and penetrates the cell (see Fig. 1 in reference [5]). Conversely, circulating soluble ACE2, while it can bind to SARS-COV2, is unable to induce cell infection. Experimentally, antibodies targeting SARS-COV seem also to block SARS-COV2 binding to ACE2, suggesting possible therapeutic strategies, notably by repositioning certain protease inhibitors [24].

Certain in-vitro studies reported a positive correlation between membrane expression and/or tissue activity of ACE2 and risk of COVID-19 infection [25]. Moreover, by binding to ACE2, the virus induces a decrease in the ACE2 tissue activity, thus aggravating COVID-19-induced inflammation in organs such as, notably, the lung [26]. One study reported decreased membrane expression of ACE2 in mouse lung following SARS-COV administration, concomitant with respiratory impairment [14]. In this context, the administration of ARB (losartan) improved respiratory function, perhaps by restoring ACE2 membrane expression and tissue activity. Thus, the level of ACE2 membrane expression and/or tissue activity may influence onset of COVID-19 infection and thus the risk of developing more severe inflammatory tissue injuries. Likewise, in a recent retrospective study of 175 Chinese COVD-19 patients requiring hospital admission, 62% showed hypokalemia, which the authors explained by altered angiotensin II deactivation by a shift in ACE1/ACE2 balance (reduced ACE2 tissue activity under COVID-19) in favour of ACE1, thus inducing aldosterone synthesis and hypokalemia occurrence [27] (Fig. 1). If this hypothesis is confirmed, mineralocorticoid receptor blockers may be able to contribute to correcting this hypokalemia.

Therefore, it is clear that ACE2 and particularly its membrane expression and tissue activity play a key role in COVID-19 infection. The exact roles, however, are complex and may be deleterious in the contamination phase, as ACE2 acts as a receptor to COVID-19 (and severity may correlate with membrane expression and tissue activity) [28,29] while being beneficial in the inflammatory lesion phase [5,30]. Many questions thus remain at present unanswered. To our knowledge, there are no pharmacologic ACE2 activators or inhibitors available to date in humans. Some groups suggested using circulating soluble ACE2 to capture as many viruses

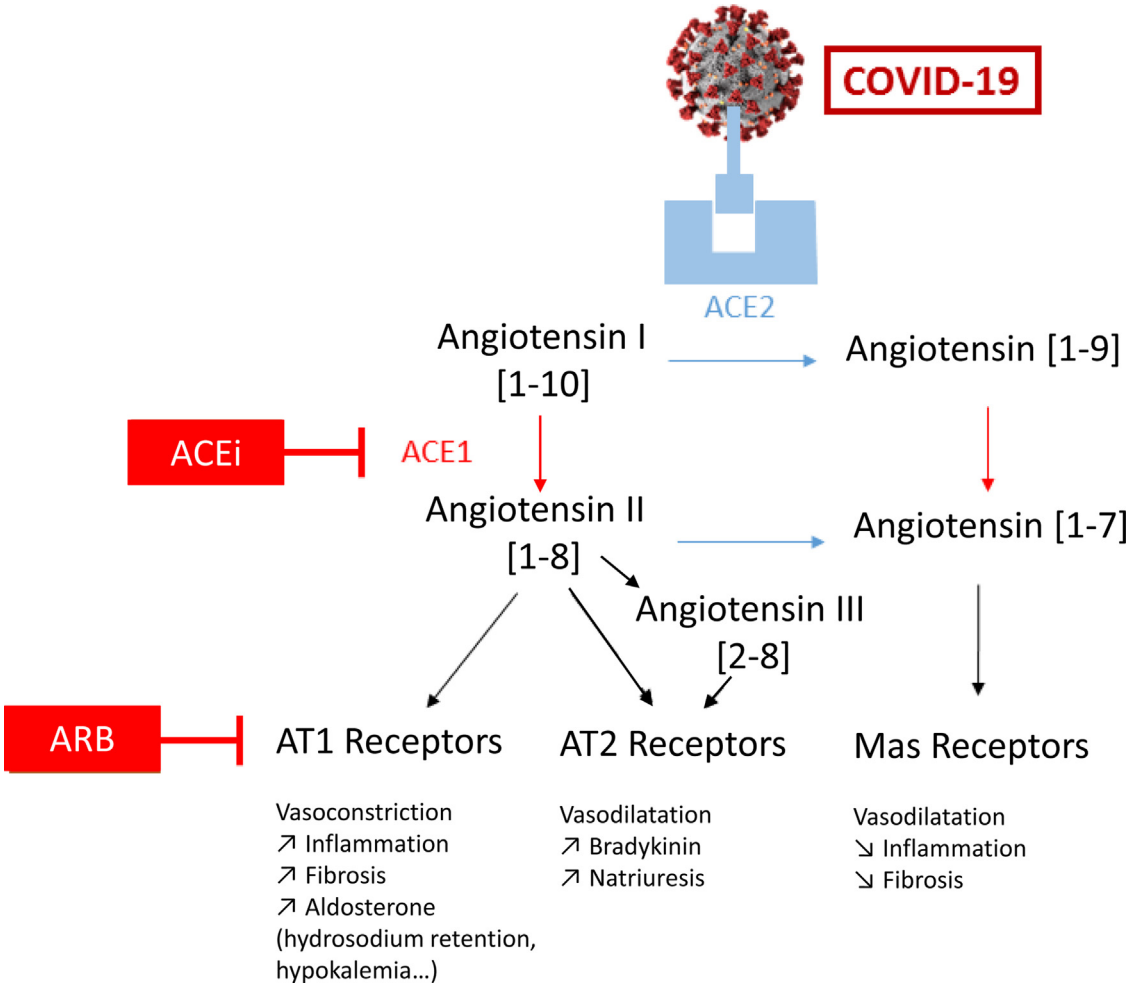

Fig. 1. General view of the renin-angiotensin-aldosterone system in the context of COVID-19 infection. ACE1: angiotensin-converting enzyme 1; ACE2: angiotensin-converting enzyme 2; ARB: angiotensin II receptor blocker; ACEi: angiotensin-converting enzyme inhibitor.

as possible in plasma, restricting their fixation on cell-membrane ACE2 and thus limiting cell infection. In-vitro studies showed that genetically engineered recombinant soluble ACE2 could be a useful therapeutic option [20,31]. Moreover, soluble ACE2 might favour the angiotensin-(1-7)/ACE2/MasR pathway over the angiotensin II/ACE/AT1R/aldosterone pathway, preventing or treating severe inflammatory tissue lesions [14]. Human recombinant soluble ACE2 is an FDA-approved treatment since 2013, with a 2017 phase-II trial in acute respiratory distress syndrome [32], which would allow rapid transfer to COVID-19. A dedicated clinical trial is to be launched soon (NCT04287686).

3. ACEi-ARB and COVID-19

Angiotensin-converting enzyme inhibitors (ACEi) principally inhibit ACE1, thus blocking angiotensin II release. (Fig. 1); action on ACE2 has never been reported, and they are thought to have no such effect [33,34]. ACEi, like ARB, are widely prescribed as maintenance therapy in several chronic cardiovascular diseases, including arterial hypertension, heart failure and diabetic nephropathy. In-vitro models free of COVID-19 reported that ACEi and ARB treatment increased membrane expression of ACE2, especially in the heart [9,16,35]. In-vitro findings in the few human studies of healthy (COVID-19-free) subjects were discordant [36–39]. It should also be borne in mind that circulating ACE2 levels may not match membrane expression and tissue activity (the latter possibly varying depending on the tissue). Certain in-vitro studies reported very low levels of circulating ACE2 despite high membrane (and thus tissue) expression [40]. There is also no evidence on the impact of ACEi/ARB on pulmonary expression of ACE2, notably in the context of COVID-19.

Some groups suggested that increased angiotensin II expression may underlie a "compensatory" response by increasing ACE2 expression; in humans, only ARBs could thus induce ACE2 elevation, as ACEis inhibit angiotensin II release [13]. Likewise, ARBs, by blocking AT1 receptors, may favour conversion of angiotensin II into angiotensin III, enhancing the benefit of AT2 receptor activation (Fig. 1). It should also be keep in mind that cardiovascular diseases themselves, and notably ischemic cardiopathy, heart failure, arterial hypertension and diabetes, were associated with increased ACE2 membrane expression and tissue activity in non-COVID-19 animal models, independently of ACEi/ARB administration [2,41–43]. The clinical situation (infection contracted, not yet contracted, patient with or without cardiovascular history and COVID-19 infection) probably plays a major role. Some studies reported high levels of ACEi/ARB in COVID-19 infection, and especially in severe forms requiring hospital or ICU admission, although it should be noticed that arterial hypertension is very common, especially in the elderly, for which ACEi/ARB is prescribed in 25–30% of cases [5]. Thus, the positive or negative impact of ACEi/ARB in COVID-19 in humans remains unknown and is complex [44], possibly even depending on clinical stage: negative in the contamination phase but beneficial in the tissue inflammation phase [45,46]. Studies of this question are forthcoming (NCT04330300).

Early data extracted from a retrospective study performed in China with potential confounders factors exhibited reassuring results with a possible beneficial effect on mortality of ACEis/ARBs [47]. Some authors suggest that ARBs but not ACEis may provide benefit in COVID-19 infection by preventing onset of severe tissue lesions [28,48]; two clinical trials of losartan (ARB) in COVID-19, with or without hospital admission, are due to be launched (NCT04312009 and NCT04311177).

Thus, many scientific societies, including the French Society of Arterial Hypertension (SFHTA) and European Society of Cardiology (see http://www.sfhta.eu/?p=6670), and many publications [5,49,50] advise against stopping maintenance treatments in an attempt to "prevent" COVID-19 infection, especially as imbalance in blood pressure and heart failure may be deleterious. There remains the difficult and unanswered question of long-course ACEi/ARB therapy in case of COVID-19 infection, especially when severe. An individual and personalised attitude seems essential, considering clinical presentation and severity (hemodynamic, respiratory and renal failure, blood pressure, etc.), and the indications for ACEi or ARB (non-complicated hypertension, heart failure with impaired LVEF, etc.). It should also be noticed that the effects of ACEi and of ARB in COVID-19 infection are unknown, and that the two may not be the same. Guidelines may be rapidly revised in the light of incoming data from ongoing clinical trials, especially concerning ARB.

Other antihypertensive and cardiovascular drugs such as dihydropyridines [51–53], the combination sacubitril-valsartan [54], thiazide diuretics [55] and mineralocorticoid receptor antagonists [56–58] affected in-vitro ACE2 tissue expression. Regarding beta-blockers, we retrieved a single in-vitro study, reporting no impact of atenolol on aortic tissue expression of ACE2 [59]. We found no studies of the impact of loop diuretics on tissue expression of ACE2, although impact is physiologically conceivable.

4. Conclusion and perspectives

The present theoretical concerns around ACE2, ACEi/ARB and COVID-19 require more detailed and dedicated human studies. It now seems clear that ACE2 is the key point for SARS-COV2 cell-entry, and it therefore represents a reasonable pharmacological target. Reducing ACE2 membrane activity and tissue expression, especially in the lung, to prevent infection or reduce severity in patients not or not yet experiencing inflammatory lesions may represent a valuable option. To prevent onset of severe inflammatory tissue lesions, especially in the lung, on the other hand, the angiotensin-(1-7)/ACE2/MasR pathway should be favoured to the angiotensin II/ACE/AT1R/aldosterone pathway in order to increase ACE2 membrane expression and/or tissue activity as pharmacological and therapeutic target (e.g., by ARBs). Circulating soluble ACE2 is also a therapeutic option that is actually evaluated. All these questions are currently unresolved and are being scrupulously investigated in ongoing trials.

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Disclosure of interest

The authors declare that they have no competing interest.

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