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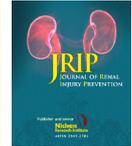


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# COVID-19 interactions with angiotensin-converting enzyme 2 (ACE2) and the kinin system; looking at a potential treatment

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## ABSTRACT

The novel coronavirus disease 2019 (COVID-19) is a rapidly expanding infection around the world. The world Health Organization (WHO) in March 2020 announced the Coronavirus pandemic. This infection causes many deaths on daily basis. Therapeutic options are currently limited. It is revealed that COVID-19 binds to human angiotensin-converting enzyme 2 (ACE2) to enter the host cells. One of the activities of ACE2 is hydrolyzing the active bradykinin metabolite [des-Arg973] BK (DABK). A decreased activity or reducing expression of ACE2 by the virus impairs the inactivation of DABK. This enhances its signaling through the bradykinin B1 receptor (BKB1R) and could lead to fluid extravasation and leukocyte recruitment to the lung. Targeting the bradykinin system by either blocking the bradykinin production or blocking bradykinin receptors may open a new potential therapeutic window for the treatment of COVID-19 induced acute respiratory distress syndrome (ARDS) particularly before patients enter the irreversible stages.

### *Implication for health policy/practice/research/medical education:*

It is revealed that Covid-19 binds to human angiotensin converting enzyme 2 (ACE2) to enter the host cells.

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## Introduction

The novel coronavirus disease 2019 (COVID-19) is a rapidly expanding infection around the globe. The Covid-19 compared to previous outbreaks of severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS) is more contagious (1). The World Health Organization (WHO) in March 2020 announced the Coronavirus pandemic (2).

This infection causes many deaths on a daily basis all over the world. Therapeutic options are currently limited. There is an emergent need for a better understanding of the pathophysiologic mechanisms to be able to prevent its fatal complications. It has been shown that COVID-19, like SARS-CoV, binds to human angiotensin-converting enzyme 2 (ACE2) via its spike glycoprotein expressed on

its envelope for entering the target cell (3-5). ACE2, which was discovered in 2000, virtually presents in all tissues with relatively higher expression in respiratory epithelial cells, alveolar cells type I and II, oral cavity, kidney, testis, and intestines (6-8). Meanwhile, using a cross-species receptor confirms a wide-host transmissibility of COVID-19, with the exclusion of chickens (9). SARS-CoV reduces the expression of ACE2 and contributes to lung injury and pneumonia (10).

## Materials and Methods

For this mini-review, we used a variety of sources including Scopus, Embase, PubMed, Web of Science and Google. The search was conducted by using combinations of the following key words and or their equivalents; COVID 19,

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SARS-CoV, bradykinin, lung injury, ACE2, Coronavirus, acute respiratory distress syndrome and angiotensin converting enzyme 2.

### Biological actions of ACE2

Renin-angiotensin-aldosterone system (RAAS) is an old and well described pathway. Over the years more discoveries revealed the involvement of RAAS in many organ dysfunction and viral infections. It is apparent now that it is even more complex than was previously thought. Production of ACE is quite ample in the human kidney at least five times more than what has been seen in the human lung (11). ACE converts angiotensin I [A(1-10)] to angiotensin II [A(1-8)] by removing two peptides from the angiotensin I. Meanwhile, via ACE2 angiotensin I converts to angiotensin 1-9. The main action of ACE2 in RAAS is to deactivate the angiotensin II (Ang II) to a peptide named angiotensin 1-7 (12,13). In fact, ACE2 acts as an endogenous counter-regulator of classic ACE system. ACE2 is not inhibited by ACE inhibitor and despite their homologous ACE2 and ACE are biochemically and pharmacologically two distinct systems (12).

Angiotensin 1-7 through its specific receptor; mas oncogene product (MAS) stimulates nitric oxide synthase (NOS) and further antagonizes Ang II action on its AT1 receptor. ACE/ACE2 ratio appears to have an important influence on different diseases including IgA nephropathy, diabetes, subtotal nephrectomy and hypertension.

Increases in the ACE/ACE2 ratio that happens during COVID-19 infection potentially influences the development of kidney damage (14). Meanwhile, ACE2 also acts on 126 biologic peptides outside the RAAS, i.e, the kinin-kallikrein system (KKS), Apelin-13 and dynorphin A peptide. These substrates could be increased and impose adverse effects with reducing the expression of ACE2 (15).

In theory, the exogenous administration of recombinant ACE2 as a therapeutic strategy to treat ARDS in COVID -19 infection might be reasonable. Exogenous administration of ACE2 in patients with ARDS did not show any difference in oxygenation index or clinical outcomes, although there was a trend of decreasing IL-6 concentrations (16). A clinical trial of administration of recombinant ACE2 in COVID -19 is under investigation now.

### Kinin-kallikrein system

In 1909, the role of kinin-kallikrein system (KKS) in decreasing blood pressure in dogs was verified (17). Bradykinin (BK) is an important pro-inflammatory peptide in that kinin-kallikrein system. It is an essential member of the vasodilators (prostaglandins, kinins and nitric oxide) that acts as a tissue hormone to regulate regional blood flow. Inflammatory mediators such as TNF- $\alpha$ , IL-4, 6, 8 and 13 via intracellular NF- $\kappa$ B and

mitogen activated protein kinase (MAPK) signal to induce bradykinin expression (18). The physiologic roles of bradykinin include propagation of inflammatory processes, vascular relaxation and interaction with regional neural structures (19). Decreased levels of bradykinin may offer some protection against ischemia/reperfusion injury during lung transplantation (15). Kinins exert their pro-inflammatory actions by the selective induction of two distinct G-protein coupled receptors, bradykinin B1 receptor (BKB1R) and bradykinin B2 receptor (BKB2R). In the kidney, BKB2R is located along the collecting duct. Bradykinin increases the blood flow within the inner medulla and inhibit the reabsorption of NaCl and has a natriuretic effect (20).

### Interaction between ACE2 and KKS

The KKS consists of high-molecular-mass kininogen (HMMK) that is proteolyzed by kallikrein to produce Bradykinin (BK) and [des-Arg<sup>973</sup>]-BK (DABK-the active metabolite of bradykinin). The former binds to bradykinin B2 (BKB2R) receptors and the later binds selectively to BKB1R.

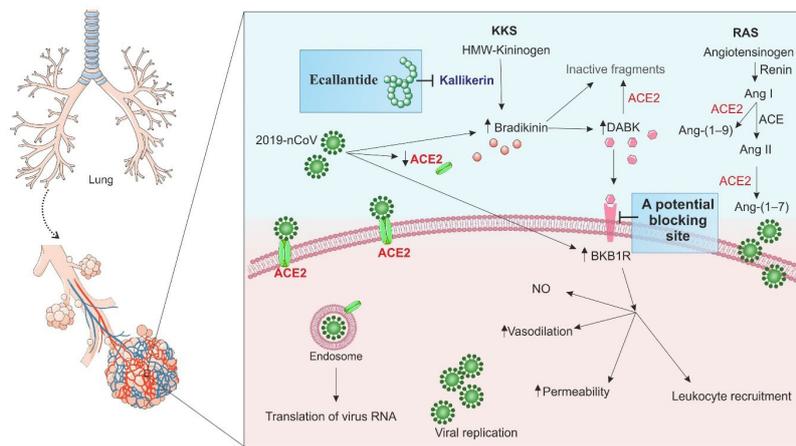
While BKB2R is constitutively expressed in multiple tissues, BKB1R is rarely expressed at baseline, is highly inducible by inflammation. In particular, BKB1R was shown to be involved in the pathogenesis of inflammatory diseases (20).

ACE2, also hydrolyzes the active bradykinin metabolite DABK(desArg<sup>9</sup>-bradykinin) (21). A decreased activity of ACE2 impairs the inactivation of DABK and therefore, enhances its signaling through BKB1R. The consequential events are fluid extravasation and leukocyte recruitment to the lung (22). BKB1R expression is also up-regulated during inflammatory conditions (23). High levels of inflammatory mediators through activation of the BK system may increase the risk of capillary permeability, ARDS, and multiple organ failure. Administration of BKB1R antagonists in experimental models of sepsis has prevented hemodynamic derangement and attenuates the risk of multi-organ failure (24).

### The proposed potential therapy

Cross-talk between RAAS and KKS systems happens via bradykinin B2 receptors. Targeting the bradykinin system by either blocking the BK production or blocking bradykinin receptors may open a new potential therapeutic window for the treatment of COVID-19 induced ARDS, particularly before patients enter the irreversible stages.

In 2009, Ecallantide was approved for the treatment of acute attacks of hereditary angioedema (25). Ecallantide selectively blocks the generation of BK from high-molecular-mass kininogen (HMMK). Icatibant is a bradykinin B2 receptor antagonist (BKB2R) which has been used in acute hereditary angioedema. Neither of those medications have been used in control of cytokine



**Figure 1. Proposed potential approach to address COVID-19 infection-induced ARDS.** ACE2 inactivates the DABK. Exposure to COVID-19, reduces the expression of ACE2 and increases the activity and level of DABK. Enhance signaling through DABK/BKB1R system leads to vascular-alveolar fluid extravasation, leukocyte extravasation, and ARDS development. Ecallantide, a 60 amino-acid recombinant protein binds to plasma kallikrein selectively and inhibits bradykinin generation from high-molecular-mass kininogen (HMMK). BKB1R: bradykinin B1 receptor, [Des-Arg973]-BK or DABK: metabolically active form of bradykinin, ACE2: Angiotensin converting enzyme 2, Ang: angiotensin, KKS: the kallikrein-kinin system, RAS: the renin-angiotensin system. ARDS: Acute respiratory distress syndrome.

storm in COVID-19 infection. On the other hand, BKB1R is only synthesized after tissue injury and up to now, despite great preclinical and experimental efforts, we do not have an available BKB1R antagonist approved for clinical use (20). Selective BKB1R blocker could be a promising agent to prevent tissue inflammation and ARDS in COVID-19 infection (24, 25) (Figure 1). In order to prove the validity, further studies and clinical trials are justified.

**Authors' contribution**

RT, AT and SZV, MRA had contribution in original draft, edit and writing the manuscript. MRA and ShG contributed to the literature search. SZV and MRA contributed to the figure design.

**Conflicts of interest**

There is no conflict of interest.

**Ethical considerations**

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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