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REVIEW

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COVID-19 Disease and Hereditary Angioedema

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ABSTRACT

Since December 2019, an outbreak of a novel coronavirus (SARS-CoV-2) infection causing COVID-19 disease has influenced the whole world. Angiotensin converting enzyme 2 (ACE2) receptors on type 2 pneumocytes in humans were determined as the entry for SARS-CoV-2. Receptor binding and subsequently endocytosis of ACE2 diminish the cell membrane expression and also the function of ACE2. ACE2 is an enzyme involved in bradykinin metabolism. Lys-des-Arg9-BK occured with enzymatic cleaving of Lys-BK derived from low molecular weight kininogen is inactivated by ACE2 in tissues and it is a vasodilator agent having its own receptor named bradykinin B1. Non-metabolized Lys-des-Arg9-BK can be the reason for tissue vasodilation and increased vascular permeability in the patients with COVID-19. Increased bradykinin levels in patients with hereditary angioedema with C1-INH deficiency (C1-INH-HAE) do not cause increased SARS-CoV-2 infection or more severe disease. Although SARS-CoV-2 infection does not result in increased bradykinin levels, it can increase Lys-des-Arg9-BK levels.

Keywords: COVID-19, SARS-CoV-2, hereditary angioedema, ACE2 receptors, bradykinin, Lys-des-Arg9-BK

Since December 2019, an outbreak of a novel coronavirus (SARS-CoV-2) infection causing SARS-CoV-2 disease has influenced the whole world. Studies have shown that COVID-19 entry is via angiotensin converting enzyme 2 (ACE2) receptors on type 2 pneumocytes in humans (Figure 1A). Receptor binding and subsequently endocytosis of ACE2 diminish cell membrane expression and also the function of ACE2. ACE2 is an enzyme, which has an important role in the renin-angiotensin and aldosterone system (RAAS). After SARS-CoV-2 binds to the ACE2 receptor, the protective effect of ACE2 against RAAS system activation significantly decreases (1).

In vitro and in vivo studies have previously revealed that a shortage of ACE2 leads to increased levels of angiotensin II, which regulates blood pressure. ACE converts angiotensin I to angiotensin II (Figure 1B) in the RAAS system. Angiotensin II is a vasoconstrictor that also has a sodium retention effect. Under normal conditions, angiotensin II is removed by ACE2. However, non-metabolized angiotensin II can cause pulmonary edema via vasoconstriction and sodium retention in SARS-CoV-2 infection. Diminished ACE2 function may result in diminished levels of angiotensin-(1-7) and angiotensin-(1-9), both have strong vasodilation effect. However, vasoconstriction is not a dominant finding in patients with COVID-19-related acute respiratory distress syndrome (ARDS). In contrast, vasodilation is the most commonly seen feature in patients with COVID-19 (2,3). How can we explain these findings?

The kallikrein-kinin system is named as the tissue kallikrein-kinin system and plasma kallikrein-kinin system depending on its location in the human body. High molecular weight kininogen cleaved by plasma kallikrein and activated Factor XII lead to the end product, bradykinin in the plasma. Low molecular weight kininogen cleaved by tissue kallikrein ends up as lys-bradykinin in the tissues (Figure 2A) (4).

Kinins have two different receptors; one of them is the inflammation upregulated B1 receptor and the other one is the constitutively expressed B2 receptor. Bradykinin (BK) and Lys-bradykinin (Lys-BK) are both ligands

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for the B2 receptor. The enzymes carboxypeptidase M (CPM) and carboxypeptidase N (CPN) can further process BK and Lys-BK into des-Arg9-BK and Lys- des-Arg9-BK, respectively. Both of them are ligands for bradykinin receptor B1. These kinins both have strong vaso-permeable and vasodilatory capacity and need to be tightly controlled to prevent excessive angioedema. The gating point for SARS-CoV-2, ACE2 is also an enzyme involved in bradykinin metabolism. Lys-des-Arg9-BK occurred with enzymatic cleaving of Lys-BK derived from low molecular weight kininogen is inactivated by ACE2 in tissues and it is a vasodilator agent having its own receptor named bradykinin B1. Non-metabolized Lys-des-Arg9-BK can be the reason for tissue vasodilation and increased vascular permeability in the patients with COVID-19. Inflammation induced higher B1 receptor levels can lead to vasodilation, vascular permeability and tissue edema, especially after several days of SARS-CoV-2 infection (Figure 2B) (5).

C1 inhibitor (C1-INH) is a serine protease that is involved in the regulation of bradykinin, a potent vasoactive substance. The reduction or absence of C1-INH synthesis results in unchecked activation of the plasma kallikrein-kinin system, which leads to the overproduction of bradykinin. Hereditary angioedema with C1-INH deficiency (C1-INH-HAE) (HAE; Online Mendelian Inheritance in Man; OMIM#106100) is a relatively rare autosomal dominant disorder that manifests as recurrent episodes of edema involving the skin (face, extremities and

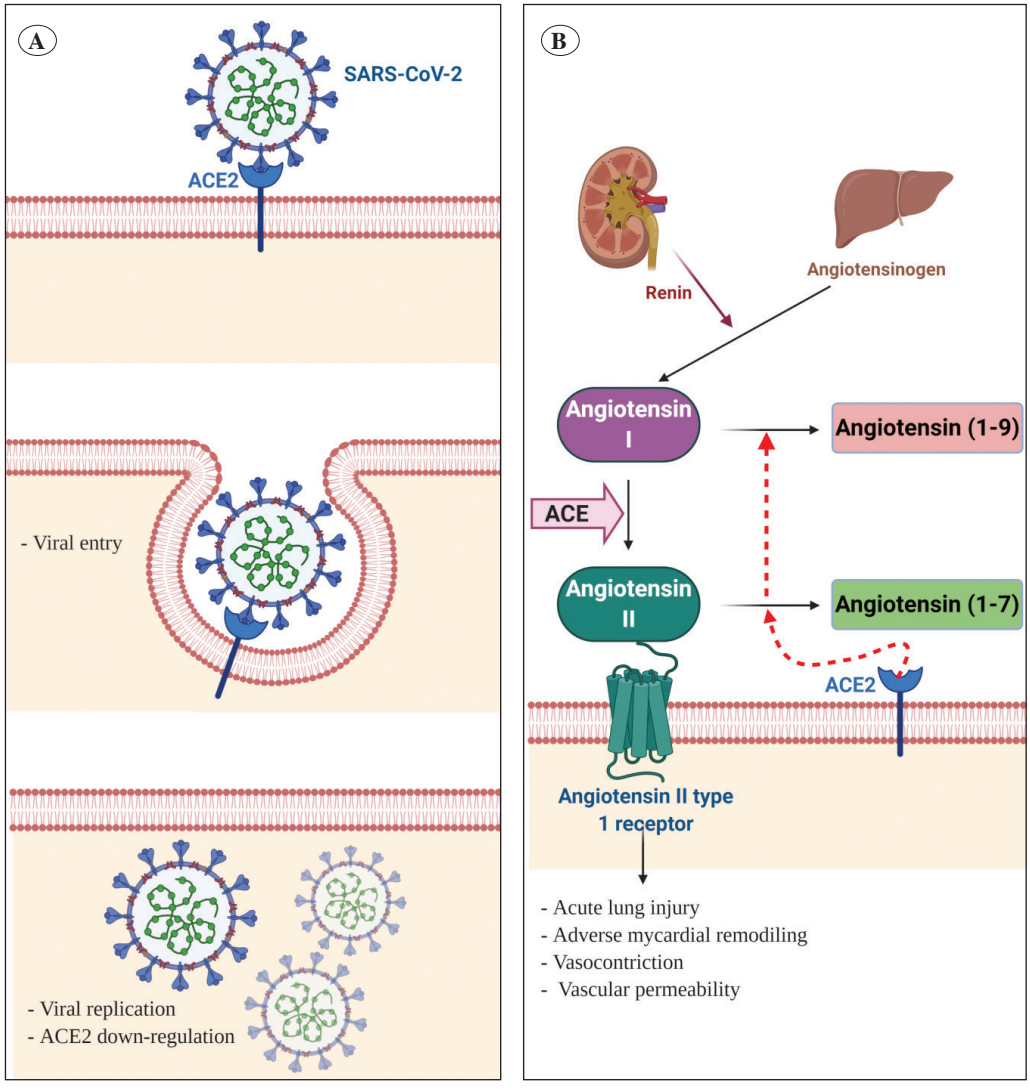

Figure 1. A) Relationship of SARS-CoV-2 and ACE2, **B)** Relationship of ACE2 and RAAS.

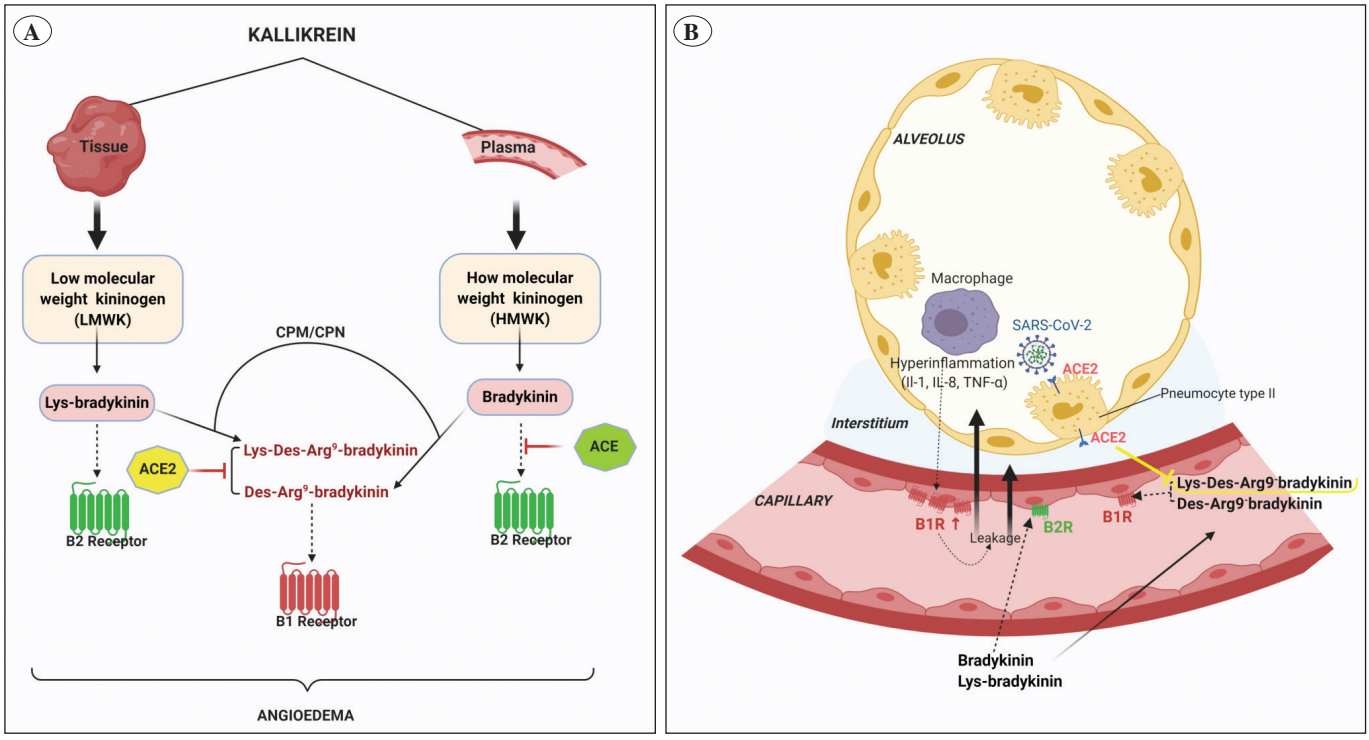

Figure 2. A) Relationship of kinin-kallikrein system and ACE2/ACE. **B)** Hyperinflammation in lung in case of severe COVID-19 developing after SARS-CoV-2 infection.

genitalia) and the mucosa (tongue, gastrointestinal tract and upper airways). Most cases of C1-INH-HAE result from mutations on the C1 inhibitor gene, *SERPING1* (MIM#606860; GenBank NM_000062), a gene located on the chromosome locus 11q12-q13.1, which leads to dysfunctional C1-INH (6,7).

After the spread of SARS-CoV-2 infection, a question came to mind. Can increased bradykinin levels in patients with C1-INH-HAE cause increased SARS-CoV-2 infection or at least more severe disease? The answer is probably not. SARS-CoV-2 infection does not result in increased bradykinin levels but it may increase Lys-des-Arg9-BK levels.

In patients with COVID-19, non-metabolized Lys-des-Arg9-BK could be the reason for tissue vasodilation and increased vascular permeability. Some studies suggest that Lys-BK also binds to the B2 receptor in addition to B1 receptor and induces vasodilation. Icatibant, the B2 receptor antagonist produced for acute attacks in C1-INH-HAE, may also be effective in ARDS related to COVID-19. Based on the same idea, the use of kallikrein synthesis inhibitors as a therapeutic agent for COVID-induced pulmonary edema can be considered. Kallikrein synthesis inhibitors, ecallantide and lanadelumab, are used in the treatment of acute attacks and prophylaxis of C1-INH-HAE, respectively (8).

Cardiovascular disease is a risk factor for the severity of SARS-CoV-2 infection. Earlier studies suggest that ACE inhibitor treatment may increase the severity of SARS-CoV-2 infection. They concluded that ACE inhibitors decrease the conversion of angiotensin I to angiotensin II, and increased angiotensin I levels may also increase ACE2 receptor expression and viral entry (9). However, in subsequent studies, it was observed that the use of ACE inhibitors did not worsen the severity of the disease. Moreover, the use of ACE inhibitors prevents angiotensin II formation and angiotensin II-related vasoconstriction. Despite the structural similarities between ACE and ACE2, their substrates differ from each other. Therefore, ACE inhibitors do not inhibit ACE2.

CONCLUSION

In summary, SARS-CoV-2 enters the human body via ACE2 receptors on type 2 pneumocytes and leads to lower cell membrane expression and function of the ACE2 enzyme. ACE2 is an enzyme involved in Lys-des-

Arg9-BK degradation in tissues. Lys-des-Arg9-BK is a vasodilator agent having its own receptor bradykinin B1. Non-metabolized Lys-des-Arg9-BK can be the reason for tissue vasodilation and increased vascular permeability in patients with COVID-19. Increased bradykinin levels in patients with C1-INH-HAE do not cause increased SARS-CoV-2 infection or more severe disease. Although SARS-CoV-2 infection does not result in increased bradykinin levels, it increases the Lys-des-Arg9-BK levels.

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