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Review Paper

A Review of the Mechanism of Action and Role of Bradykinin in Severity of COVID-19 Symptoms

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ABSTRACT

Over a year has passed since the diagnosis of the first coronavirus disease 2019 (COVID-19) case in Wuhan, China. After that, this disease spread worldwide and infected people with a spectrum of symptoms, the most important and fatal of which are respiratory symptoms. Kinins, particularly bradykinin, are responsible for many respiratory functions, including vasodilation, vasoconstriction, and regulating permeability in vessels and lung tissue. The present study aims to review the bradykinin synthesis and degradation process, its mechanism of action, and its contribution to pulmonary function. Also, we investigate the role of bradykinin in treating and reducing the severity of COVID-19 symptoms. Results indicate that engagement of angiotensin-converting enzyme 2 (ACE2), a factor contributing to vasomotion and vascular permeability, as a result of virus entrance and its failure to inactivate des-Arg9-bradykinin (DABK) along with infiltration of proinflammatory cytokines, leads to increased vascular permeability and pulmonary edema. Consequently, inhibition of DABK synthesis or activity through blockade of the type 2 bradykinin receptors can help manage pulmonary edema.

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Introduction

It has been over a year since the diagnosis of the first coronavirus disease 2019 (COVID-19) case, and its pandemic has spread worldwide. During this period, people in different countries have been infected by this virus and experienced various symptoms, from fatigue and pain to respiratory disorders and even death. Numerous studies have been conducted to determine the effect of the virus on the human body and the development of the symptoms.

According to the results, different factors contribute to the disease symptoms, including kinins with their roles in respiratory disorders. Bradykinin (BK) and its derivatives control vascular permeability, dilation, and inflammation through increasing receptors for these kinins. BK and des-Arg9-bradykinin (DABK) binding to their specific receptors result in higher vascular permeability and potential pulmonary edema. The virus enters the cell through the angiotensin-converting enzyme 2 (ACE2) receptor. This receptor plays a crucial role in preventing pulmonary edema by deactivating DABK. Hence, virus binding to ACE2 reduces its capacity to inactivate DABK [1].

Moreover, the elevated level of hyaluronic acid and its associated water absorption impairs gas exchange and exacerbates the disease symptoms [2]. Therefore, the current review investigates the function and mechanism of action of bradykinin and its derivatives, exploring their relationships to COVID-19 symptoms and examining treatment approaches based on bradykinin modulation.

Kinin-kallikrein system (KKS)

Bradykinin, one of the Kinin-Kallikrein system's essential inflammatory peptides, reduces blood pressure [3]. BK acts as a tissue hormone for regulating local blood flow and other vasodilators such as prostaglandins, kinins, and nitric oxide (NO). Inflammatory mediators, including tumor necrosis factor-α, interleukin (IL)-4, IL-6, IL-8, IL-3, nuclear factor kappa-light-chain-enhancer of activated B cells, and mitogen-activated protein kinase signal for the BK expression [4], exerting its inflammatory processes through vascular relaxation and interaction with local neuronal structures [5]. Reduction of BK can protect against ischemia and perfusion change [6]. The inflammatory effect of kinins is through two distinct G-protein coupled receptors: Type 1 and 2 bradykinin receptors (B1R and B2R). In the kidney, B2Rs are located along collecting tubes. Via these receptors, BK increases perfusion in the medulla and prevents renal sodium reabsorption. Therefore, this hormone has a natriuretic effect [7].

Interaction between ACE2 and KKS

KKS comprises high-molecular-weight kininogen (HMWK) proteolyzed by kallikrein, yielding BK and DABK—active metabolites—binding to their specific receptors. While B2R is expressed in various body tissues, B1R expression highly depends on inflammation. In general, B1R contributes to the pathogenesis of inflammatory diseases [7].

ACE2 results in the degradation of DABK [8], and its reduced activity causes diminished inactivation of DABK. Hence, B1R improves DABK signaling, leading to the accumulation of fluids and infiltration of leukocytes into the lung tissue [9]. Accordingly, B1R antagonists prevent impaired hemodynamics and multi-organ failure [10].

Physiological function of bradykinin

BK is a nano-peptide, usually found in the blood in its inactive form. BK serves as a potent vasodilator and physiological mediator of anaphylactic shock arising from mast cells' activation and release after binding specific antigens to IgE on mast cells' membranes [11].

Regulation of pulmonary vascular tone is vital for pulmonary function. The renin-angiotensin system (RAS) regulates the vasodilation and vasoconstriction of pulmonary vessels. BK and kinins are responsible for the permeability and vasodilation of these vessels. Increasing evidence states that BK contributes to COVID-19 respiratory symptoms such as dry cough. Persistent dry cough is one of the common side effects of angiotensin-converting enzyme inhibitors (ACEis), seen in 35% of patients treated with these inhibitors [12-15]. Research in this context indicates elevated BK's significant role in dry cough resulting from ACEis [15-17]. Inflammation increases B1R receptors in the lungs. The binding of BK and DABK to their receptors, ie, B2R and B1R, respectively, increases vascular permeability and pulmonary edema [18, 19].

Furthermore, BK stimulates the coughing reflex by activating B2Rs [20]. COVID-19 can result in acute respiratory distress syndrome (ARDS) through the pulmonary bradykinin pathway [18, 19]. Studies show that COVID-19 infection reduces ACE levels and increases ACE2 levels. The latter is responsible for the inactiva-

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tion of DABK to prevent pulmonary edema. Virus binding to ACE2 attenuates its ability to inactivate DABK [1, 9, 21], leading to increased BK. In addition to BK, the hyaluronic acid level also increases, and its degrading enzymes decrease. Water absorbed by hyaluronic acid and increased fluid leakage to the lungs form a gel-like material hindering pulmonary gas exchange in the lungs, giving rise to severe COVID-19 complications. Besides pulmonary injury, through BK and DABK pathways, the virus can also bring about brain damage. BK has two receptors, though the number of B1Rs in the brain and spinal cord is low. More B2Rs are present in the brain. BK is a substrate for ACE rather than ACE2 [9, 22]. Systemic hypertension through the B2R receptor results from BK injected to the lateral cerebral ventricle [22]. DABK is a substrate for ACE2 and binds to B1R. Also, people with hypertension, diabetes, heart failure, and obesity show more B1Rs [23]. Therefore, the severity of COVID-19 symptoms is higher in these people. Increased B1R expression leads to higher oxidative stress in the brain (by releasing NO and converting peroxynitrite to free radicals) and impaired blood-brain barrier. The spike protein of the virus poses similar effects [23, 24]. In addition, increased B1Rs in the brain are accompanied by more release of norepinephrine, leading to severe central and peripheral hypertension [25]. Additionally, BK stimulates sensory neurons of respiratory tracts through elevated synthesis of prostaglandin (PG)I2 and PGE2 [17].

Bradykinin synthesis and degradation

Kininogen 1 (*KNG1*) encodes low and high-molecular-weight kininogen. Both proteins emerge from various modifications of the same gene based on the tissue conditions. High-molecular-weight kininogen (HK) degradation by plasma kallikrein releases BK, and low-molecular-weight kininogen (LK) degradation by tissue kallikrein releases lysyl-BK. Both kinins are recognized by B2R present in vascular endothelium. Shortening of BK or lys-BK using carboxypeptidase M of tissue or carboxypeptidase N of plasma drastically changes the characteristics of kinin, and the resulting products DABK and DA-lys-BK binding to B1 receptor present in various cell types, including leukocyte and endothelial cells present in inflammation site. Proinflammatory cytokines stimulate B1R expression, and there is evidence of cytokine storm during COVID-19 infection, highlighting the role of B1R [19, 26, 27].

In physiologic conditions, BK and lys-BK have a short half-life in plasma, and both are degraded directly in plasma. Thus, BK effects are localized, and its vascular filtration and hypotension are prevented. The inactivation of BK in plasma mainly depends upon its degradation by ACE. Also, dipeptidyl peptidase 4 decomposes aminopeptidase P metabolites. Therefore, ACE inhibition increases BK half-life in plasma. It must be reminded that dry cough is a side effect of medicine-induced ACE inhibition. The same complication is observed in COVID-19 patients. In some cases, BK-induced angioedema is seen in this treatment. Therefore, plasma-dependent production of BK is regulated by ACE, and probably, the same mechanism that relates the fibrinolytic system to the plasma system improves BK production in COVID-19 infection and intensifies disease symptoms [28-33].

Bradykinin signaling

The bradykinin signaling pathway illustrated in Figure 1 can be summarized as follows: SARS-CoV-2 virus enters the cell through the ACE2 receptor. Infection by this virus reduces ACE2 expression in the plasma membrane of infected cells, leading to elevated levels of DABK in the extracellular environment of infected cells and neighboring ones. This kinin contributes to the inflammation of the airways. COVID-19 infection severely affects host cell hemostasis by triggering endoplasmic reticulum stress, mitochondrial death signal, downregulation of ACE2 and upregulation of proinflammatory genes, and cell death signaling. Cellular injury and inflammation induce upregulation of B1R and migration to the plasma membrane results in DABK-induced inflammation and damage. Tissue injury and inflammation bring about increased BK levels and stimulation of B2R. The hypothesis regarding impaired BK signaling in COVID-19 respiratory problems is that low ACE2 expression leads to the accumulation of DABK in the extracellular environment of infected cells and their neighboring. It will create a positive feedback loop of inflammation and injury, leading to even higher DABK levels, BK-induced injury, and inflammation. In addition to strong binding to B1R, DABK weakly binds to B2R in specific tissues. It can be supposed that using DABK positive-feedback loop inhibitors can alleviate inflammatory effects, and better results can be achieved in COVID-19 treatment [34].

Role of bradykinin in COVID-19 infection

It is claimed that disease severity and most deaths are due to local vascular problems emanating from the activation of B1Rs on lung endothelial cells. ACE2 receptor is a membrane-bound molecule with enzymatic activity. Besides its role in RAS, it is necessary for the inactivation of DABK, the ligand for B1R (Figure 2). Compared to B2R, B1R is upregulated on endothelial cells by pro-

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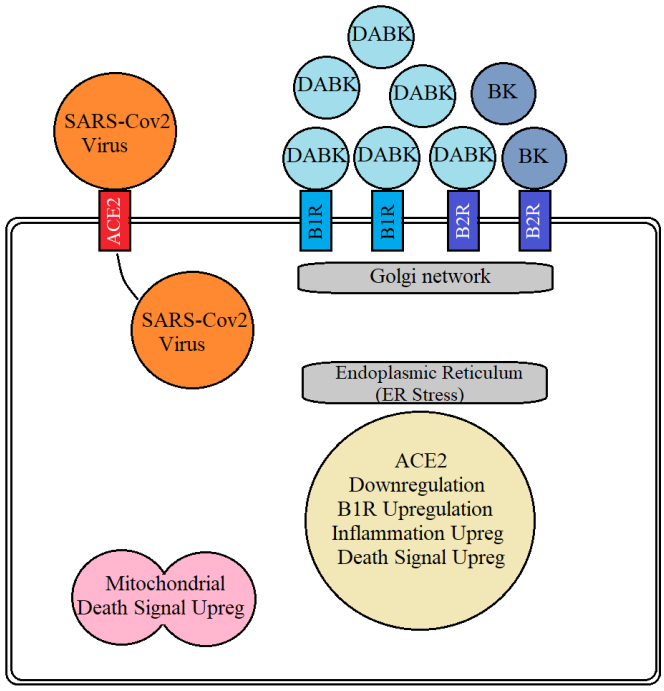

Figure 1. Bradykinin signaling pathway during COVID-19 infection

inflammatory cytokines. Without the function of ACE2 as a protection for the inactivation of B1R ligands, the lung will be susceptible to local vascular leakage, leading to angioedema. This complication is probably present at the onset of the disease and can justify common scans and the sense of being drowned experienced by patients. In some patients, the complication is accompanied by worsening clinical conditions during day 9 due to antibody production against virus spike protein. This antigen binds to ACE2 and contributes to disease severity by improved infiltration of local immune cells and proinflammatory cytokines. In severe cases, elevated levels of serum proinflammatory cytokines, including IL-6, Il-2R, and IL-1β, are reported [35].

In parallel, inflammation prompts increased B1R expression, and possibly, along with worsened viral infection due to antibody production, ACE2 function is weakened in the presence of the virus. In this context, it can be argued that BK-induced local pulmonary angioedema through B1 and B2 receptors is a crucial characteristic of COVID-19, accounting for many ICU admissions. Therefore, the inhibition of B1 and B2 receptors has a relieving effect on COVID-19 symptoms. Kinin-dependent pulmonary edema is resistant to corticosteroids and adrenalin and must be taken seriously throughout the viral infection. Furthermore, this pathway may be indirectly sensitive to the anti-inflammatory agents or strategies for neutralizing the spike's anti-antibody response. However, it is insufficient for completely eliminating pulmonary edema [36]. BK exerts vascular function through two receptors. Type 2 receptor strengthens eNOS binding to calcium-calmodulin at a Ca^{2+}-based level. In this way, nitric oxide (NO) output is similar to iNOS. Moreover, if endothelial cells are invaded, eNOS-derived NO prevents microbial growth and is sufficient for independent immunity of endothelial cells. Unfortunately, owing to the reduced expression of B2R, BK-induced vasodilation decreases considerably with age. Hence, the relationship between age and COVID-19 risk can be justified [37].

Bradykinin-based treatment strategies

Mechanistic similarities between pulmonary edema in COVID-19 and hereditary angioedema (HAE) imply that treatment based on inhibition of DABK function or formation can be beneficial for managing COVID-19 edema. There are numerous choices for HAE treatment, such as B2R inhibition using icatibant (B2R antagonist) and lanadelumab (plasma kallikrein inhibitor). However, more evidence is needed to approve these treatments in COVID-19 cases [12, 38-40].

In COVID-19 infection, the fundamental assumption is the dysfunction of ACE2 that increases the half-life of DABK or LDABK. Since ACE2 is present in plasma, it affects the half-life of DABK in patients' plasma and determines blood antigen levels [41]. Another key assumption is that DABK is the primary mediator for

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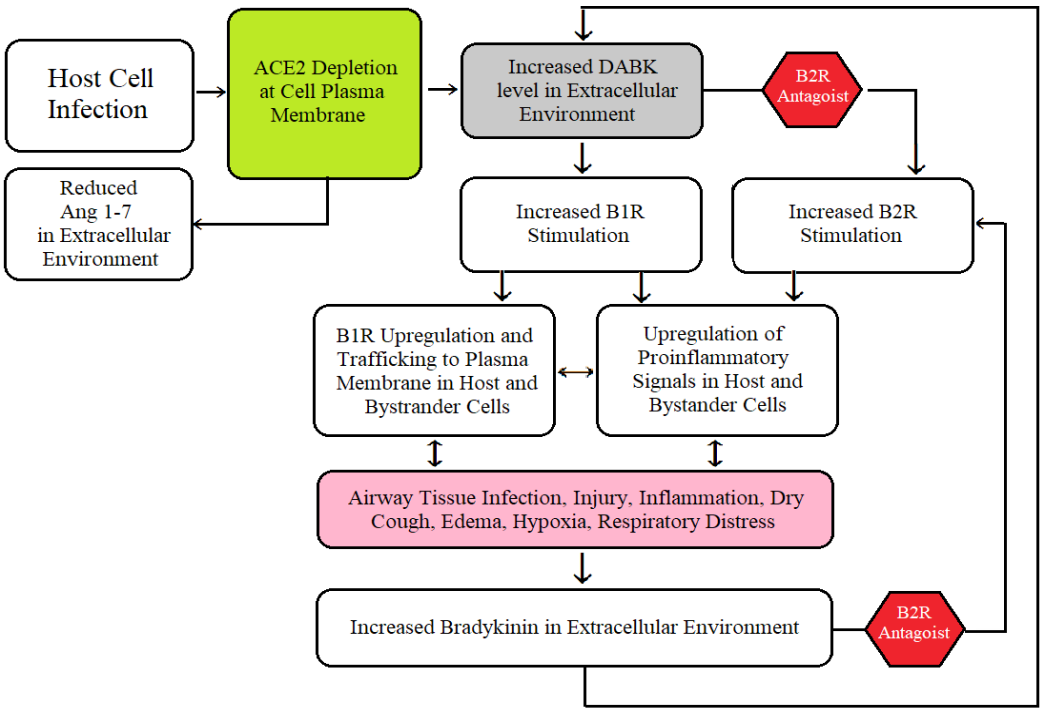

Figure 2. Hierarchy of events following COVID-19 infection

activating B1R and its subsequent pulmonary edema rather than LDABK (Lys-Des-Arg9-bradykinin). In this case, DABK is probably produced by activating the plasma contact system. If LDABK is responsible, it is synthesized by tissue kallikrein, and hence, it cannot be controlled by traditional HAE treatments [8]. It is assumed that pulmonary edema due to ACE2 dysfunction results from elevated levels of angiotensin II. However, experiences show no difference in hydrostatic pressure, and the high level of angiotensin II is ruled out as the cause of pulmonary edema [1]. Still, BK elevation with no increase in hydrostatic pressure can explain this phenomenon. ACE2, a part of the BP decrease axis by RAS, increases BK activity through elevation of angiotensin production.

On the other hand, ACE, a key part of blood pressure control, increases the axis through RAS, degrades BK, and limits its function [34]. Previous research reported that symptoms and signs reported for COVID-19 patients result from elevated BK storm [34, 36, 42]. BK storm occurs when the ACE2 level falls in the body, resulting in elevated DABK levels and pulmonary injury and inflammation [25]. Reduction of ACE2 results in continuous vasoconstriction, developing into tissue damage [34, 43]. Elevated DABK level gives rise to ER stress, mitochondrial death signal, downregulation of ACE2, and upregulation of proinflammatory genes, which drive the cell toward apoptosis [34]. Through upregulation of B1R, cell injury intensifies the response and strengthens DABK-induced inflammation and damage [34, 44]. In this way, a positive feedback loop of inflammation and injury develops [45]. Garvin et al. stated that genetic analysis of lavage and bronchoalveolar fluids taken from COVID-19 patients shows reduced ACE expression and improved ACE2, angiotensin, renin, primary RAS receptors, kininogen, kallikrein, and B1R and B2R expression. They noted that in lung cells, COVID-19 causes an 8-fold reduction of ACE expression level and a 99-fold improvement of ACE2 expression [2]. As a consequence, elevated BK level in most tissues is predictable, and corresponding outcomes, including improved permeability and vasodilation, hypotension [16], hypokalemia [46], arrhythmia, and sudden cardiac death [47], ensue. Most of these complications are reported in COVID-19 patients. Notably, the renin-angiotensin-aldosterone system (RAAS) system controls vasodilation and vasoconstriction, BK controls permeability and vasodilation, while ACE2 controls both [21].

To verify the role of kinins in COVID-19 pathogenesis, combined data with clinical evaluation of HAE treatments is needed. None of the approved medications show direct antagonistic effect on bradykinin. However, some researchers reported a synergic effect of raloxifene and bradykinin. Indeed, mice treated with raloxifene show a further reduction of systolic blood pressure, indicating more accessible NO in treated animals [48]. Stud-

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ies evaluating the effect of theophylline [49], inhaled sodium cromoglycate [50], indomethacin [51], sulindac [52], aspirin [53], calcium channel blockers [51], and ferrous sulfate [54] on dry cough induced by ACE inhibitors introduced indomethacin as the only medication effectively alleviates this complication. Indomethacin (50 mg, BID) can reduce or even terminate ACE inhibitor-induced dry cough in 96% of patients [51].

The bilateral relationship between RAAS and KKS systems is through B2Rs. Based on what is explained above, targeting the BK system via inhibition of BK synthesis or its receptors can be a treatment strategy for ARDS developed due to COVID-19 infection, particularly when the patient has not entered the irreversible phase yet [14]. In what follows, the possible role of two medications is described.

Possible role of indomethacin

Besides its essential effect as a non-selective cyclooxygenase inhibitor, indomethacin reduces inflammatory conditions arising from abnormal elevation of bradykinin. A growing number of studies denote the role of bradykinin in COVID-19 symptoms and indomethacin's role in lowering dry cough in these patients [55]. Though the contribution of bradykinin to dry cough is not thoroughly understood, the available data point to the main role of elevated PGI2 and PGE2 inflammatory prostaglandins [15]. PGI2 and PGE2 are key mediators of inflammation, pain, and fever, mainly produced by COX enzymes, inhibiting by indomethacin [56]. Indomethacin also inhibits phospholipase A2, another enzyme producing PGI2 and PGE2 [57].

Possible role of ecallantide

Ecallantide is a medication used for HAE acute attacks [58]. While ecallantide has not been tested for the treatment of COVID-19, it can be considered an alternative for its inhibitory effect on BK synthesis and alleviation of disease complications [7].

Conclusion

This review examined the role of bradykinin and its derivatives and receptors in developing COVID-19 symptoms and available treatment strategies for alleviating COVID-19 complications. To consider treatment strategies applicable to COVID-19 patients, further evidence must be gained on the efficiency of these treatments and then used as choices for those suffering from COVID-19 respiratory complications. Additionally, a better understanding of the function of bradykinin and other proinflammatory cytokines in inflammatory reactions to COVID-19 infection is mandatory for determining effective treatments. Also, understanding the systemic pathway enables the limitation of tissue damage resulting from the disease, and one is better prepared to prevent severe inflammatory reactions induced by these molecular signals.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

The both authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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