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Research Article

The Role of Bradykinin and Bradykinin-Related Peptides in COVID-19: A Review

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ABSTRACT

Introduction: This article discusses the global impact of COVID-19, caused by SARS-CoV-2, highlighting its symptoms, treatments, and preventive measures. It focuses on the involvement of the Kallikrein-Kinin System (KKS) and its interaction with the Renin-Angiotensin System (RAS), which contribute to the pathophysiology of severe respiratory syndrome in infected patients.

Materials and methods: This study used an integrative literature review approach, searching PubMed and Google Scholar for articles on bradykinin, COVID-19, SARS-CoV-2, and the Kallikrein-Kinin and Renin-Angiotensin systems. Studies published in the last five years were prioritized, with qualitative analysis performed.

Results: This integrative review included over 15 articles focusing on the interaction between Bradykinin (BK), SARS-CoV-2, and related systems such as the Kallikrein-Kinin System (KKS) and Renin-Angiotensin System (RAS). It highlights that SARS-CoV-2 activates these systems, triggering BK storms, increased vascular permeability, and inflammation, contributing to pulmonary edema and severe symptoms. Studies also show that viral proteins activate the KKS, intensifying BK production. B2 receptor antagonists (e.g., icatibant) and kallikrein inhibitors are promising treatments, yet more research is needed to evaluate their effectiveness and potential therapeutic benefits in COVID-19 management.

Conclusion: This study suggests that SARS-CoV-2-induced ACE2 downregulation triggers a bradykinin storm, contributing to COVID-19's pathophysiology. B2 antagonists show potential.

Keywords: SARS-CoV-2; Kinins; Renin-angiotensin system; COVID-19

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged in December 2019 in the city of Wuhan, China, spreading rapidly around the world, filling hospitals and killing millions of people across the world. declared a pandemic in March 2020. The disease had more than 774 million positive cases and 7.0 million deaths recorded worldwide by the first months of 2024. This virus has become a real problem mainly due to its high degree of transmissibility and aggressiveness. Some patients may experience classic symptoms such as fever, dry cough, loss of smell and taste, while others develop more serious symptoms such as pulmonary edema, acute respiratory distress syndrome, pulmonary thrombosis and hypoxemic respiratory failure, which can lead to the patient's death [1].

The treatment of COVID-19 was based on symptomatic relief, such as the use of antipyretics, analgesics and antitussives. In more serious clinical conditions, the use of oxygen therapy and mechanical ventilation was adopted to promote respiratory support. In addition, anticoagulants have also been seen as auxiliary in their administration in cases of risk of clot and thrombus formation in the complications of the disease. Furthermore, monoclonal antibodies (immunobiologicals) with different targets have recently been used to treat severe cases. In this way, it has become protocol to follow behaviors that are ways of avoiding transmissibility, such as isolation, the use of face masks and the proper handling of hand sterilization with soap or

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70% alcohol. In this regard, the greatest advance in the face of COVID-19 as a form of prevention has been the production of vaccines that have succeeded in ensuring efficiency in preventing severe forms of the disease, thus reducing the mortality rate [2].

SARS-CoV-2 belongs to the Coronaviridae family and the betacoronavirus genus. It is protected by a nucleocapsid and consists of a lipid bilayer envelope that surrounds its single-stranded RNA. The virus has proteins related to viral structuring and release (E), assembly and shape determination (M) and viral replication (N). Moreover, in the virus envelope there are spike glycoproteins containing 2 functional subunits S1 and S2, with projections on the surface in the shape of a crown of thorns, which are responsible for viral attachment and entry into host cells. Through the S1 subunit of this protein, the epithelial cells of type II pneumocytes are infected by SARS-CoV-2 through interaction with Angiotensin Converting Enzyme II (ACE2). This enzyme, a homologue of Angiotensin Converting Enzyme (ACE), is mainly responsible for the cleavage of vasoconstrictive angiotensin II into vasodilatory angiotensin 1-7 and for the production of aldosterone after stimulation of the adrenal glands in the zona glomerulosa, and is negatively regulated after interaction with the virus. ACE and ACE2 are zinc-dependent metallopeptidases that act in the metabolism of peptides, forming part of two systems, the Renin Angiotensin System (RAS) and the Kallikrein Kinin System (KKS). Thus, in the presence of the virus, ACE2 is inactivated in the plasma membrane and both systems and their peptides are deregulated and overexpressed, contributing to pulmonary edema and favoring the pathogenesis of the disease [3].

With the global health problem caused by COVID-19, it was discovered that Bradykinin (BK) and its active metabolite Des-Arg-9-BK (DABK) are related to most of the clinical and pathological manifestations caused by the virus. In this context, it has been observed that excessive BK and DABK can complicate SARS-CoV-2 infection due to increased vascular permeability, release of pro-inflammatory cytokines and chemokines such as: TNF-α, IFNs, MCP-1, IL-6, IL-8, IL-1, which together promote the recruitment and activation of immune cells. Furthermore, this increase in BK and its active metabolites is related to the exacerbation of the cough reflex, which is in fact often found as one of the symptoms of the disease. Therefore, this review aims to discuss the involvement of KKS, including BK and its active metabolites, and the relationship between KKS and RAS in severe acute respiratory syndrome caused by SARS-CoV-2 [4].

MATERIALS AND METHODS

Kallikrein-Kinin system

The Brazilian physician Mauricio Rocha e Silva discovered bradykinin as an inflammatory mediator in 1949. He identified a hypotensive and vasodilating peptide in animals when he isolated a substance present in the venom of the Bothrops jararaca snake. BK and Kallidin (Lys-BK) are two kinins of the Kallikrein-Kinin System (KKS) that are formed from the cleavage of high molecular weight and low molecular weight kininogens through the activation of plasma kallikrein and tissue kallikrein, respectively. DABK and Lys-des-arg-9-BK (Lys-DABK) are active metabolites formed after the cleavage of BK and Lys-BK by carboxypeptidases N and M, present in cell membranes and plasma [5].

In plasma, the half-life of BK is smaller than 30 seconds and it is degraded to an inactive fragment by the ACE enzyme, which prevents systemic vascular leakage. Meanwhile, DABK can have a half-life of 20 minutes, for example, and is inactivated by ACE2. BK and its active metabolites act through two receptors, the B2 receptor and the B1 receptor, respectively. Both of them are G protein-coupled receptors containing 7 transmembrane domains. The B2 receptor is expressed continuously in various tissues, while the B1 receptor is poorly expressed under physiological conditions, since it is usually induced by inflammatory cytokines (IL-6, IL-8, IL-1β) and tissue injury. Once BK and its active metabolites bind to their receptors, various functions are regulated, such as blood pressure, control of vascular homeostasis, promotion of vasodilation and vascular permeability. All these factors induce natriuretic effects and promote exudation in endothelial cells and tissues [6].

BK is one of the main mediators of the KKS, since this system communicates with others, such as the RAS, the coagulation system and the complement system. The KKS is an endogenous cascade that includes a complex of enzymes, kininogenases and glycoproteins called kininogens. Kininogens are synthesized in the liver. They are present in various organs, including the vascular wall of blood vessels. Moreover, high molecular weight and low molecular weight kininogen are two types of kininogen and each kininogen has several extracellular domains in its structure with different functions.

The kininogenases are serum enzymes that are present in the plasma as plasma kallikrein and in the tissues as tissue kallikreins. Plasma prekallikrein is a zymogen, synthesized by the liver and secreted into the circulation as an inactive protein, it travels through the vessels bound to the domain 6 of the high-molecular-weight kininogen and coagulation factor XI. The Hageman factor (FXII) transforms inactive prekallikrein into active plasma kallikrein. Plasma kallikrein can work as a coadjuvant by modulating inflammation, leading to neutrophil aggregation and activating the alternative complement pathway. Furthermore, in cells tissue kallikrein is synthesized and secreted by various organs as an active enzyme in tissues, and found in the kidneys, arteries, lungs, pancreas, salivary glands and immune cells [7].

The activation of the CCS happens through two pathways, the FXII-independent pathway of the coagulation cascade and the FXII-dependent pathway. The dependent pathway occurs when FXII is transformed into its activated form FXIIa after contact with anionic biological surfaces, such as blood contact with the vascular endothelium, neutrophil extracellular networks or inorganic polyphosphates released by activated platelets. The formation of FXIIa activates the intrinsic coagulation pathway, and modifies prekallikrein into plasma kallikrein, which cleaves HMWK to produce bradykinin.

In the independent pathway, prekallikrein and FXII bind to a complex in endothelial cells formed by the urokinase Plasminogen Activator Receptor (uPAR) and cytokeratin 1 receptor. This links up with the HMWK bound to gC1qR, a receptor for the globular heads of C1q, which is part of complement. A protein, prolylcarboxypeptidase, activates plasma prekallikrein when it is bound to this component, originating BK *via* HMWK. Besides, FXII is converted into the activated forms FXIIa and FXIIf. FXIIf does not participate in coagulation, but it does participate by activating the complement cascade, as it binds to the C1r receptor. In addition, FXII and plasma kallikrein are inhibited by the serpin C1 esterase inhibitor (Figure 1) [8].

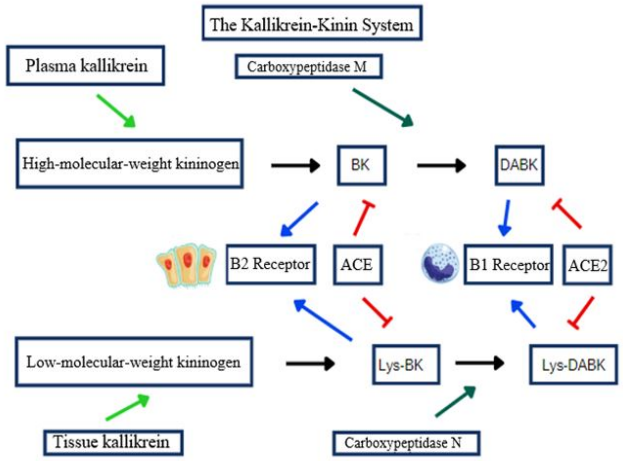


Figure 1: KKS flowchart.

The plasma kallikrein acts on high molecular weight kininogen, transforming it into BK, which in turn is converted into DABK by the action of carboxypeptidase M. The low molecular weight kininogen, through the action of tissue kallikrein, is transformed into Lys-BK and subsequently into Lys-DA, by way of carboxypeptidase N. ACE has the role of inactivating both BK and Lys-BK and ACE2 acts to inactivate DABK and Lys-DABK. Finally, BK and Lys-BK bind to the B2 Receptor and DABK and Lys-DABK bind to the B1 Receptor (Figure 2).

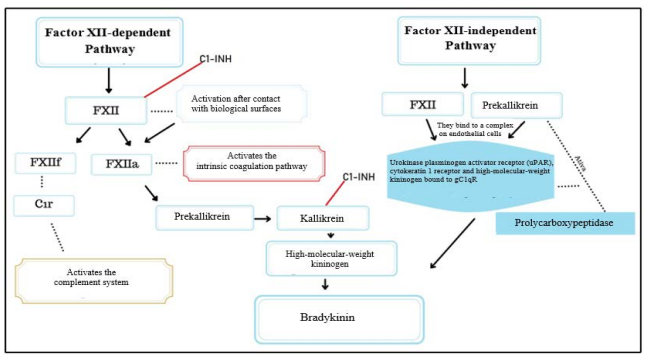


Figure 2: KKS activation flowchart.

Interaction between the renin angiotensin system and the Kallikrein Kinin system

The RAS performs important actions, regulating blood pressure, blood volume and acting on blood vessels, through two metallopeptidases, ACE and ACE2, this system is also involved with the CCS. ACE1 and ACE2 show 61% similarity, however they are different and have different active targets. ACE is a transmembrane peptidyl dipeptidase, which is expressed in various tissues such as endothelial cells and the lungs. Its function is the formation of Angiotensin II (Ang II), an active vasoconstrictor. It also acts in the inactivation of BK and Lys-BK peptides. Moreover, ACE has a greater affinity for BK, suggesting that ACE degrades more BK than it produces Ang II.

ACE2, homologous to ACE, is a metallocarboxyl peptidase expressed in type II pneumocytes in the lungs and in various tissues. The function of ACE2 is to hydrolyze various peptides, such as Angiotensin I into Angiotensin 1-9 (Ang 1-9), Ang II into Angiotensin 1-7 (Ang 1-7), as well as the peptide analogues of BK, DABK and Lys-DABK [9].

The degradation of Ang II into Ang 1-7 decreases the pro-inflammatory and pro-thrombotic vasoconstrictive effects by activating its AT1 receptor and, as a result, tissues are protected against damage, including lung damage. Ang 1-7 induces protective effects by binding to its MAS receptor and also increases vasodilation through the B2 kinin receptor. Thefore, the formation of Ang II is reduced, as is the degradation of bradykinin. In addition, ACE inhibitors, also potentiate the vasodilating effects of BK, as does Ang 1-7.

Finally, BK and Ang II bound to their respective B2 and AT1 receptors are physiological antagonists, since binding to the AT1 receptor mediates vasoconstriction and prothrombotic effects, whereas the B2 kinin receptor mediates vasodilation and antithrombotic effects. The B1 kinin receptor and the AT2 receptor also induce different functions in relation to each other (Figure 3).

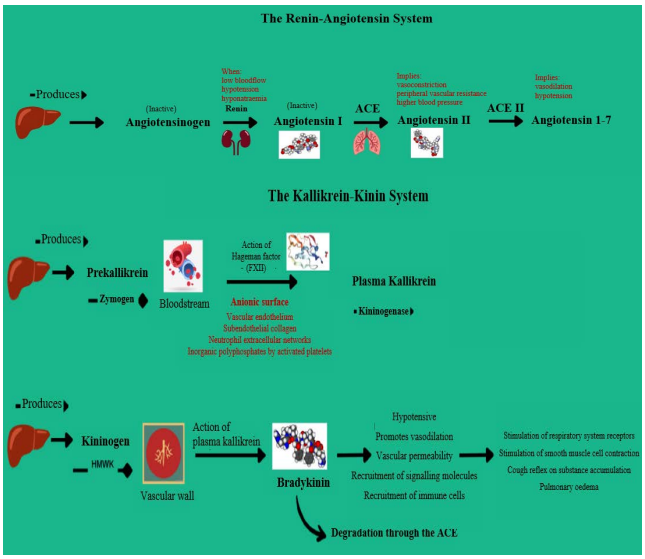


Figure 3: Flowchart of the activation of the various systems.

This study employed the integrative literature review method, as described by Ercole, Melo, and Alcoforado, which allows for the synthesis and analysis of key evidence on a specific research problem. An integrative review is particularly useful for compiling existing knowledge and identifying trends or gaps in the literature.

Data collection was conducted through searches in the PubMed and Google Scholar databases, using the following search terms: "Bradykinin", "COVID-19", "SARS-CoV-2", "Kallikrein-Kinin system", "Renin-angiotensin system", and their English equivalents. The search was limited to articles published in the last five years, but older studies were also included if they provided essential background information on the systems under investigation.

Inclusion criteria focused on studies directly addressing the interaction between bradykinin, SARS-CoV-2, and the Kallikrein-Kinin and renin-angiotensin systems. Articles that did not meet these criteria or were not available in full text were excluded. Additionally, only studies published in English and Portuguese were considered.

The selected studies were analyzed qualitatively, with emphasis on comparing methodologies, results, and key findings. The information was categorized into central themes, allowing for a broader understanding of the literature's contributions regarding the impact of these physiological systems on COVID-19.

RESULTS

It is evident that a sample of at least 15 articles were included in the development of the results of this integrative review. In this way, we selected materials available in the scientific literature that are consistent with the subject matter that reveals the involvement of bradykinin and its active metabolites, as well as the relationship between the KKS and RAS in the severe acute respiratory syndrome caused by SARS-CoV-2.

It is evident that the primary entry factors for the SARS-CoV-2 virus into cells are ACE2 and transmembrane serine protease (TMPRSS), both of which are cell surface components. Although ACE2 and its co-receptors are found in the lower airways, it has been revealed that they are also expressed in the upper airways, especially in the nasal mucosa. While TMPRSS cleaves the spike protein to prepare for cell fusion, the ACE2 receptor allows viral entry by binding to the spike protein, which promotes endocytosis. Consequently, as bonds with ACE2 will be generated, this enzyme will become less expressed in the plasma membrane of infected cells. ACE also has its levels decreased in COVID-19, due to the high amounts of Ang II, a product of ACE and, because this enzyme has its levels decreased in COVID-19, the ability to degrade BK is compromised. In addition, quantitative analyses of mRNA from bronchoalveolar lavage samples of COVID-19 patients showed that the *SERPING1* gene encoding C1-INH is 33 times less expressed in these patients compared to uninfected individuals. This is highly significant, since C1NH is an inhibitor of FXII and plasma kallikrein, and therefore low levels of this protein would lead to a substantial loss of downregulation in the coagulation cascade and bradykinin synthesis in COVID-19 patients.

This means that BK and its active metabolites DABK and Lys-DABK would be free to bind to the B1 and B2 kinin receptors, thus triggering a bradykinin storm. The activation of the B2 receptor by BK induces an increase in vascular permeability in endothelial cells, resulting in vascular leakage, accumulation of fluid in the tissues, activation of the intrinsic coagulation pathway and recruitment of pro-inflammatory cells, leading to pulmonary oedema. This dysregulation resulting from exudation in endothelial cells is observed in severe COVID-19 patients and there is a possibility that it is a consequence of the actions of BK and plasma kallikrein.

Moreover, some studies suggest that the infection caused by the virus in the organism can induce the production of pro-inflammatory cytokines, due to the hyperactivation of the B1 kinin receptor, implying pathophysiological processes that generate exacerbated inflammation and tissue damage. Thus, this could result in a cytokine storm and induce acute lung injury and subsequent severe acute respiratory syndrome.

A review study published in 2020 reported that cells infected with SARS-CoV-2 have increased the synthesis and expression of the gC1qR protein as well as High Molecular Weight Kininogen (HMWK). In addition, gC1qR favourably induces the B1 kinin receptor.

It is well known that plasmin, not only acts in fibrinolysis, but also induces the activation of FXII, which starts the cascade of the intrinsic pathway with the activation of pre-Kallikrein, contributing to the formation of BK. These findings indicate that gC1qR, HMWK and plasmin may be activating the SCC and intensifying the production of BK, and the active peptides DABK and Lys-des-arg-9-BK in COVID-19 patients.

In vitro trials conducted by Savitt and colleagues tested recombinant SARS-CoV-2 proteins to check if they activated the complement and KKS systems. More specifically, the study aimed to check whether the viral proteins (S1, N and M) were able to bind directly to the gC1qr protein, FXII and HMWK using assays. They showed that the higher the concentration of viral proteins, the higher they bound to HMWK, gC1qR and FXII. In this way, it has been experimentally confirmed that SARS-CoV-2 can induce the activation of the SCC, and the activation of the intrinsic coagulation pathway. Furthermore, since the activation of SCC and FXII gave rise to BK, the assays revealed that the amount of BK increased proportionally to the increase in viral protein concentrations up to 5 ug/ml. Nevertheless, at a higher concentration (10 ug/ml), a drop in BK levels was observed. The authors justified these results due to the probable rapid formation and degradation of BK, as its half-life is short in plasma and it is rapidly inactivated by ACE, but this does not mean that there is actually less generation of BK.

Savitt et al., carried out a pre-incubation in the haemolysis test using water, IgG antibody as a positive control and normal human serum from donors. Next, they added erythrocytes to test whether the viral proteins could bind directly to C1q, which is the protein that initiates the classical complement pathway, as

well as to C4d, which is present in the classical pathway cascade. However, the test indicated that there was no haemolysis at any of the concentrations, because the viral proteins, the IgG antibody and gC1qR all bound to C1q, sequestering it. As a result, when red blood cells were added there was no destruction, as no C1q left available. Therefore, other tests were carried out to verify the deposition of C1q and C4d, and these showed that the membrane proteins of the virus, as well as the nucleocapsid, bind strongly to C1q, while the envelope protein binds to the C4d fragment. Consequently, *in vitro* results have shown that viral proteins participate in activating the CCS and the complement system, through gC1qR, which could lead to a BK storm in COVID-19 patients.

Jakwerth and colleagues, observed that since ACE2 is a multifunctional enzyme, that is, it involves systems such as RAS and KKS, it was possible to understand the reason why the severe course of the disease was not restricted to the lungs, but systemically. They carried out a cohort study of 66 COVID-19 patients admitted to the Intensive Care Unit (ICU) and found that the KKS was highly activated, resulting in the consumption of factor XII, prekallikrein and High Molecular Weight Kininogen (HMWK). This means that a strong indication of the actual production of kinins was indeed present.

Moreover, an experiment was also conducted using NHBEs (Normal Human Bronchial Epithelial Cells) infected with SARS-CoV-2. On the basal side of the cell, a B2 receptor antagonist was introduced, approved in 2010, icatibant. A control standard was also separated from the experiment. Then, they infected the apical side of both cell groups with SARS-CoV-2. Subsequently, they noted that the epithelial layers remained qualitatively more intact when using icatibant, which strengthened the protective indication for the bronchial epithelium when using the B2 receptor antagonist.

DISCUSSION

The metallocarboxyl peptidase ACE2, a homologue of ACE, has a crucial function in viral infections that affect the lungs, such as infections caused by SARS-CoV-2 viruses, as it is the main gateway to host cells. The expression of ACE2 is reduced in the presence of the virus, leading to its negative regulation in the cell's plasma membrane. This occurs because the virus's S protein binds to the ACE2 receptor, internalising itself and thus contributing to the pathogenesis of the disease.

One study sought to identify an ACE2 substrate *in vivo* in airway epithelial cells and to verify the effects of this substrate on lung inflammation, induced by an inflammatory mediator, the endotoxin Lipopolysaccharide (LPS). The findings indicate that ACE2 is downregulated in the lung, due to the infiltration of proinflammatory cells induced by LPS, and this decrease prevented the degradation of the BK peptide analogue, DABK, which, when activated, upregulated the B1 kinin receptor, leading to exacerbated inflammation and lung injury. As mentioned above, BK and its active metabolites are inflammatory mediators and thus induce the release of proinflammatory cytokines and the shedding of plasma proteins such as those of the complement system, thereby promoting bronchoconstriction, bronchospasm, airway inflammation and pulmonary oedema.

Another study carried out by Gavin et al. to analyse the gene expression of cells in the bronchoalveolar lavage fluid of severe COVID-19 patients showed that ACE expression levels are decreased, as mentioned above. Nevertheless, the expression of ACE2 genes is high due to a genetic compensation mechanism in the body and this, however, triggers an overproduction of BK, causing a storm of this kinin. The analyses also revealed that the levels of hyaluronic acid are increased in COVID-19, and the enzymes that degrade it are attenuated. This acid can be converted into a hydrogel when it absorbs liquid. Interestingly, in COVID-19, there is endothelial deregulation by the action of BK's active peptides, suggesting that vascular leakage can lead to the formation of a hydrogel and be the cause for the failure to allow oxygen in and carbon dioxide out of the lungs of patients with the disease.

The experimental research performed by Savitt et al. as described above, proposed that gC1qR can bind to the virus in its intracellular form or when it is being secreted. In this way, the immune system would not recognise SARS-CoV-2, which can further trigger the activation of the complement system and SCC, resulting in potent complement fragments C3a and C5a, as well as a bradykinin storm, which together contribute to the pathogenesis of the disease. Additionally, the researchers assume that when cells are infected, there is a release of gC1qR, and when it binds to C1q, it promotes the initiation of the classical complement pathway. Moreover, the study suggests that the viral proteins remain intact in the plasma and bind to gC1qR after the virus has been eliminated, so that the SCC and complement can be constantly activated, which would explain the persistent symptoms that some patients report such as coughing, shortness of breath, fatigue and others.

It is believed that SARS-CoV-2 can trigger the activation of different systems other than the SCC, such as complement and coagulation, and thus contribute to the formation of powerful peptides, as well as degradation products that culminate in systemic inflammation, endothelitis, coagulopathy, pulmonary oedema and intravascular thrombosis. In fact, several biomarkers used in COVID-19, such as D-dimer and prothrombin time, which are products involved in the degradation of fibrin, have been shown to be elevated, confirming that the coagulation system is activated. Furthermore, increased levels of BK may explain the dry cough in COVID-19, since BK can irritate the airways and cause coughing. This symptom can be compared to the classic adverse effect of some ACE inhibitor drugs, which result in the deposition of Lys-BK in the tissues and BK in the plasma, which can cause a dry cough, as well as angioedema in hypersensitive individuals. In hereditary angioedema, there is a deficiency of C1-INH and, as a result, plasma kallikrein and FXII can induce activation of the KKS and complement system, which promotes excessive formation of BK and DABK. However, in angioedema caused by ACEI, there is a decrease in BK degradation, but not an increased production, resulting in a dry cough that is mediated by the action of Lys-BK on the smooth muscles of the bronchi, contracting them.

Finally, several drugs are being analysed for the treatment of COVID-19. In the study by Jakwerth et al., the efficacy of the B2 receptor antagonist was demonstrated from various perspectives. In order to replicate SARS-CoV-2 infection in mice, IL-12 was introduced intranasally to simulate inflammation in the airways *via* the IL-12/IFN-γ axis. Thus, a control group and a group with the introduction of a B2 receptor antagonist were separated. At the end of the test, it was realised that treatment with the B2 receptor antagonist caused a significant drop in ACE2 levels. They repeated the test, but with a real SARS-CoV-2 infection in human NHBEs, separating a control cell group and one treated with a B2 receptor antagonist. At the end of the test, they were able to notice that the treated group had total RNA and genomic viral RNA levels reduced by the B2 receptor antagonist. Thus, since the virus is also capable of promoting its own entry at cellular level by affecting G Protein-Coupled Receptor signalling (GPCRs) and impacting on the physiology of ion transporters such as sodium and potassium, the use of B2 receptor antagonists has also proved effective in counter-regulating the local ionic imbalance in the airways and the cellular signalling processes *via* GPCRs. In this way, the entry, replication and spread of the virus is impaired.

In Roche and Roche's study in 2020, the drug icatibant, approved by the FDA in the United States for the therapy of patients with hereditary angioedema and ACEI-induced angioedema, was shown to be useful in mitigating the effects that BK and DABK cause and reducing the respiratory distress of COVID-19 patients. The active substance in the drug is a B2 kinin receptor antagonist (named HOE-140), so it acts by inactivating the B2 receptor by preventing the binding of BK. Another drug that may be favourable is Ecallantide, approved for the treatment of hereditary angioedema, which acts by inhibiting plasma kallikrein. However, this drug is very expensive and needs to be administered by a healthcare professional in a suitable location to avoid anaphylactic reactions. That's why more studies are needed to offer more perspectives on the treatment of COVID-19.

Moreover, the monoclonal antibody called Lanadelumab, used by patients suffering from hereditary angioedema attacks, also acts by inhibiting plasma kallikrein, and thus helps to prevent the production of kinins, and the bradykinin storm.

Finally, as well as B2 receptor antagonists, the drug BI-1113823, a B1 receptor antagonist, also looks promising for combating COVID-19. This is because it acts by reducing DABK levels in endothelial cells, but it has not yet been approved.

CONCLUSION

The results of this study strongly suggest that the downregulation of ACE2 induced by SARS-CoV-2 leads to hyperactivation of the CCS and RAS. This results in a bradykinin storm, as well as activation of the complement, coagulation and fibrinolytic systems, which play a critical role in the pathophysiology of COVID-19. It is important to emphasise that the studies carried out in this research aim to contribute to understanding the mechanisms that COVID-19 causes in the human body, seeking to develop an effective treatment, as well as demonstrating the feasibility of using B2 receptor antagonists, which is also the bradykinin-binding receptor itself.

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