



Bradykinin System: A Therapeutic Goal for COVID-19

Leila Hosseini ¹, Javad Mahmoudi ¹, Saeed Sadigh-Eteghad ¹ and Mojtaba Ziaee ^{2, 3, *}

¹Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

²Medicinal Plants Research Center, Maragheh University of Medical Sciences, Maragheh, Iran

³Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

*Corresponding author: Medicinal Plants Research Center, Maragheh University of Medical Sciences, Maragheh, Iran. Email: mjziaee@gmail.com

Received 2020 August 16; Revised 2020 October 18; Accepted 2020 November 01.

Keywords: Pharmacotherapy, Bradykinin, Covid-19, Pharmacotherapy

Dear Editor,

We would like to provide some novel therapeutic approaches to the COVID-19 pandemic crisis. With the global spread of COVID-19, finding novel applications for available medications could be beneficial in the current critical phenomenon. Although there is not a standard and reliable treatment for the recent COVID-19 pandemic, we decided to search for it due to its importance.

As a novel infectious disease, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2 or COVID-19) appeared in Wuhan, China, in December 2019 and broadly spread to other parts of the world (1). According to the latest global statistics, six million people in the world have been infected with this virus, with 400,000 deaths worldwide. The main symptoms of COVID-19 consist of fever, dry cough, shortness of breath, pulmonary edema, and myalgia or fatigue (2). As known, SARS-CoV-2 enters cells via angiotensin-converting enzyme 2 (ACE2) receptors. This route plays a key role in the pathogenesis of COVID-19 and the development of Acute respiratory distress syndrome (ARDS) (3, 4). It has been shown that anti-ACE2 antibodies and ACE2 inhibitors can block the SARS-CoV invasion (5, 6).

Bradykinin (BK), a linear nonapeptide, is extensively distributed in plasma and different tissues and formed by the enzymatic activity of kallikrein on kininogens. Kallikreins are divided into plasma kallikrein and tissue kallikrein (7). Various peptidases such as ACE (also known as kininase II) and carboxypeptidases (N and M) can degrade BK into inactive fragments. Bradykinin regulates plasma exudation, chronic inflammatory reactions, and nociception, and can trigger the dilatation of blood vessels through the release of prostacyclin, nitric oxide, and endothelium-derived hyperpolarizing factor; besides, it increases vascular permeability, ultimately leading to edema formation (8, 9). Kinins transduce their biologic effects through the stimulation of G protein-coupled receptors, which are divided into two groups including BK B1 and B2

receptors. The agonists for the BK B2 receptor are BK and Lys-bradykinin, while des-Arg-bradykinin and des-Arg-Lys-bradykinin bind to the BK B1 receptor (10).

It has been demonstrated that the SARS-CoV infection depletes ACE2 that leads to increased levels of [des-Arg(9)]-bradykinin (DABK), a bioactive metabolite of BK and a potent ligand of the BK B1 receptor in the lung that is related to lung injury and inflammation (11, 12). High levels of inflammatory cytokines upregulate the B1 receptor on endothelial cells and through the activation of the BK system, may increase the risk of capillary permeability and angioedema (13). Bradykinin-mediated angioedema consists of three angioedema types:

- 1) Hereditary angioedema (HAE),
- 2) Acquired C1-inhibitor deficiency
- 3) ACE inhibitor-associated angioedema.

The C1-inhibitor (C1-INH), a key protease inhibitor in the complement system, is involved in the regulation of numerous serine proteases, such as contact system protease (plasma kallikrein), early proteases of the classical and lectin complement systems (C1r/s, MASP1 and 2), coagulation factor XIa, plasminogen, and vascular permeability. As known, C1-INH dysfunction can cause inappropriate activation of the contact system with the excessive generation of kallikrein, resulting in the proteolysis of high molecular-weight kininogen and eventually the production of BK (14). Besides, HAE, an autosomal dominant disease, is caused by either a mutation in the gene encoding C1-INH or decreased C1-INH protein levels (15). In patients with acquired C1-INH deficiency, the catabolism of C1-INH increases (16). Bradykinin is inactivated by ACE, but ACE inhibitors can block the inactivation of BK by ACE, leading to an increase in its biological activity and enabling to induce angioedema (17) (Figure 1).

Possible Pharmacotherapy:

-Icatibant: Icatibant acetate (Firazyr) is a selective and competitive, synthetic inhibitor of the B2 BK receptor. Pre-

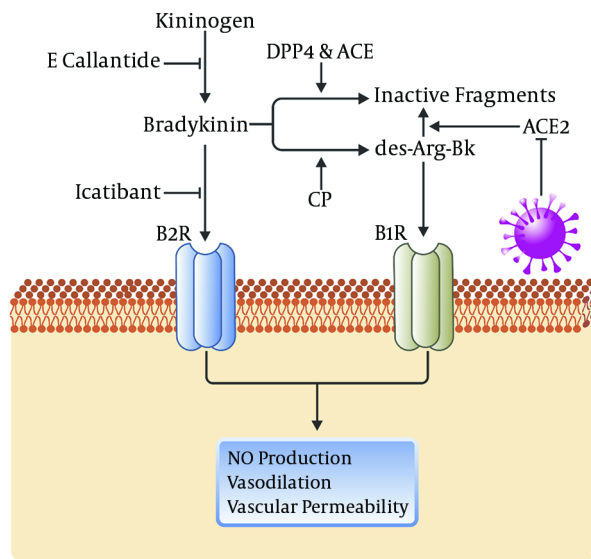


Figure 1. The schematic pathways involved in bradykinin (BK)-mediated angioedema.

vious randomized controlled clinical trials (phase 3) evaluated the efficacy of this drug on HAE. Icatibant administration may relieve the symptoms of angioedema and improve the overall situation in all patients after 0.5-11 hours. In 40% of patients, therapeutic goals were achieved in less than four hours (18, 19). Icatibant prepared as prefilled 30 mg syringes can be administrated by subcutaneous injection; the mean time to maximum plasma concentration (T_{max}^c) was 1.79 h and the mean maximum plasma concentration was 405 ng/ml. (20) Common adverse effects are elevated liver enzymes, injection reaction, dizziness, headache, nausea, and fever (21).

-Fresh Frozen Plasma (FFP): The FFP contains varying amounts of C1-INH. It has been recommended for HAE and ACE inhibitor-mediated angioedema (22). The efficacy of FFP has been reported in reducing ICU stay duration and intubation frequency (23, 24). There is a theoretical controversy about the clinical application of FFP in COVID-19 patients because it contains substrates such as kallikrein and kininogen that may elevate bradykinin levels and worsen the condition of patients. Despite this hypothetical impact, FFP has not worsened symptoms in similar angioedema patients. Recent reports suggest the effectiveness of cured COVID-19 patients' plasma in the treatment of severely ill patients. Thus, FFP can be suggested as a possible treatment for further clinical studies. It should be considered that FFP could exert some side effects such as hypersensitivity reactions or may worsen angioedema and transfusion infection (25).

-Ecallantide: Ecallantide (Kalbitor) is a recombinant inhibitor of kallikrein that is made available as 3 ml vials and approved for use in HAE (26). This protein prevents bradykinin production from kininogen. A recent placebo-controlled clinical trial named EDEMA demonstrated that the administration of 40 mg/m² ecallantide could improve the symptoms of angioedema in four hours although other doses did not (27). They suggested subcutaneous injection as an effective route in comparison with IV application. Common adverse effects of ecallantide are headache, injection site reactions, nausea, and fever while hypersensitivity and anaphylaxis could be considered life-threatening phenomena (28).

-Berinert and Cinryze: These medications provide the endogenous plasma protein that controls the function of kallikrein and factor XII, reducing the level of bradykinin. Berinert and Cinryze are concentrated C1-INH collected from healthy blood donors. The mechanism of action of these molecules is the regulation of kallikrein and factor XII activity and the reduction of bradykinin production (29). One previous study showed that the mean time of angioedema reversal in 18 HAE patients was 42.2 minutes (22). The main side effect of these medications could be hypersensitivity, thrombosis, and blood-borne infection.

As mentioned above, ARDS is well known as the main death cause of COVID-19-infected patients. Central pathophysiologic features of ARDS include dysregulated inflammation, inappropriate recruitment, the activity of leukocytes and platelets, uncontrolled activation of coagulation pathways, and altered permeability of alveolar endothelial and epithelial barriers. Kawasaki et al. reported that DPP4 inhibition by sitagliptin attenuated LPS-induced lung injury in mice, as confirmed by inhibiting pro-inflammatory cytokines IL-1 β , TNF- α , and IL-6 (30).

In summary, due to the increased spreading of the disease and its high mortality, there is an urgent need to find effective treatments. The role of the kallikrein-kinin system in the pathogenesis of COVID-19 has been less examined. We suggest that the severity of the disease and its high mortality are because of vascular problems owing to the activation of B1 and B2 receptors on endothelial cells in the lungs and dysregulated BK; thus, blocking these receptors or decreasing the production of BK might be effective in COVID-19 treatment. We propose that targeting BK may open a new potential therapeutic window for the treatment of COVID-19.

Footnotes

Authors' Contribution: All authors equally contributed to the work. Hosseini wrote the introduction and Ziaee hypothesized the manuscript and reviewed the manuscript and corrected it. Mahmoudi and Sadigh wrote pharmaceutical sections.

Conflict of Interests: The authors of this paper declare no financial competing interests.

Funding/Support: None

References

- Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2020;**41**(2):145–51. doi: [10.3760/cma.j.issn.0254-6450.2020.02.003](https://doi.org/10.3760/cma.j.issn.0254-6450.2020.02.003). [PubMed: [32064853](https://pubmed.ncbi.nlm.nih.gov/32064853/)].
- Munoz J. Covid-19 epidemic: Exercise or not to exercise; that is the question!. *Asian J Sports Med*. 2020;**11**(1). doi: [10.5812/asjms.102630](https://doi.org/10.5812/asjms.102630).
- Imai Y, Kuba K, Penninger JM. Angiotensin-converting enzyme 2 in acute respiratory distress syndrome. *Cell Mol Life Sci*. 2007;**64**(15):2006–12. doi: [10.1007/s00018-007-6228-6](https://doi.org/10.1007/s00018-007-6228-6). [PubMed: [17558469](https://pubmed.ncbi.nlm.nih.gov/17558469/)]. [PubMed Central: [PMC7079778](https://pubmed.ncbi.nlm.nih.gov/PMC7079778/)].
- Naksuk N, Lazar S, Peeraphatdit TB. Cardiac safety of off-label COVID-19 drug therapy: a review and proposed monitoring protocol. *Eur Heart J Acute Cardiovasc Care*. 2020;**9**(3):215–21. doi: [10.1177/2048872620922784](https://doi.org/10.1177/2048872620922784). [PubMed: [32372695](https://pubmed.ncbi.nlm.nih.gov/32372695/)]. [PubMed Central: [PMC7235441](https://pubmed.ncbi.nlm.nih.gov/PMC7235441/)].
- Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*. 2003;**426**(6965):450–4. doi: [10.1038/nature02145](https://doi.org/10.1038/nature02145). [PubMed: [14647384](https://pubmed.ncbi.nlm.nih.gov/14647384/)]. [PubMed Central: [PMC7095016](https://pubmed.ncbi.nlm.nih.gov/PMC7095016/)].
- Huentelman MJ, Zubcevic J, Hernandez Prada JA, Xiao X, Dimitrov DS, Raizada MK, et al. Structure-based discovery of a novel angiotensin-converting enzyme 2 inhibitor. *Hypertension*. 2004;**44**(6):903–6. doi: [10.1161/01.HYP.0000146120.29648.36](https://doi.org/10.1161/01.HYP.0000146120.29648.36). [PubMed: [15492138](https://pubmed.ncbi.nlm.nih.gov/15492138/)].
- Ghahestani SM, Mahmoudi J, Hajebrahimi S, Sioofy-Khojine AB, Salehi-Pourmehr H, Sadeghi-Ghyassi F, et al. Bradykinin as a probable aspect in SARS-Cov-2 scenarios: Is bradykinin sneaking out of our sight? *Iran J Allergy Asthma Immunol*. 2020;**19**(S1):13–7. doi: [10.18502/ijaa.v19i\(S1\).2850](https://doi.org/10.18502/ijaa.v19i(S1).2850). [PubMed: [32534506](https://pubmed.ncbi.nlm.nih.gov/32534506/)].
- Marcelino-Rodriguez I, Callero A, Mendoza-Alvarez A, Perez-Rodriguez E, Barrios-Recio J, Garcia-Robaina JC, et al. Bradykinin-mediated angioedema: An update of the genetic causes and the impact of genomics. *Front Genet*. 2019;**10**:900. doi: [10.3389/fgene.2019.00900](https://doi.org/10.3389/fgene.2019.00900). [PubMed: [31611908](https://pubmed.ncbi.nlm.nih.gov/31611908/)]. [PubMed Central: [PMC6776636](https://pubmed.ncbi.nlm.nih.gov/PMC6776636/)].
- Mahmudpour M, Roozbeh J, Keshavarz M, Farrokhi S, Nabipour I. COVID-19 cytokine storm: The anger of inflammation. *Cytokine*. 2020;**133**:155151. doi: [10.1016/j.cyt.2020.155151](https://doi.org/10.1016/j.cyt.2020.155151). [PubMed: [32544563](https://pubmed.ncbi.nlm.nih.gov/32544563/)]. [PubMed Central: [PMC7260598](https://pubmed.ncbi.nlm.nih.gov/PMC7260598/)].
- Bjorkqvist J, Sala-Cunill A, Renne T. Hereditary angioedema: a bradykinin-mediated swelling disorder. *Thromb Haemost*. 2013;**109**(3):368–74. doi: [10.1160/TH12-08-0549](https://doi.org/10.1160/TH12-08-0549). [PubMed: [23306453](https://pubmed.ncbi.nlm.nih.gov/23306453/)].
- Roche JA, Roche R. A hypothesized role for dysregulated bradykinin signaling in COVID-19 respiratory complications. *FASEB J*. 2020;**34**(6):7265–9. doi: [10.1096/fj.20200967](https://doi.org/10.1096/fj.20200967). [PubMed: [32359101](https://pubmed.ncbi.nlm.nih.gov/32359101/)]. [PubMed Central: [PMC7267506](https://pubmed.ncbi.nlm.nih.gov/PMC7267506/)].
- Sodhi CP, Wohlford-Lenane C, Yamaguchi Y, Prindle T, Fulton WB, Wang S, et al. Attenuation of pulmonary ACE2 activity impairs inactivation of des-Arg(9) bradykinin/BKb1R axis and facilitates LPS-induced neutrophil infiltration. *Am J Physiol Lung Cell Mol Physiol*. 2018;**314**(1):L17–31. doi: [10.1152/ajplung.00498.2016](https://doi.org/10.1152/ajplung.00498.2016). [PubMed: [28935640](https://pubmed.ncbi.nlm.nih.gov/28935640/)]. [PubMed Central: [PMC5866432](https://pubmed.ncbi.nlm.nih.gov/PMC5866432/)].
- Jurado-Palomo J, Caballero T. Pathophysiology of bradykinin-mediated angioedema: The role of the complement system. In: Kartal SP, Kutlubay Z, editors. *The role of the complement system a comprehensive review of urticaria and angioedema*. Rijeka-Croatia: Intech Open Access Publisher; 2017. p. 151–76. doi: [10.5772/67704](https://doi.org/10.5772/67704).
- Cugno M, Zanichelli A, Foieni F, Caccia S, Cicardi M. C1-inhibitor deficiency and angioedema: molecular mechanisms and clinical progress. *Trends Mol Med*. 2009;**15**(2):69–78. doi: [10.1016/j.molmed.2008.12.001](https://doi.org/10.1016/j.molmed.2008.12.001). [PubMed: [19162547](https://pubmed.ncbi.nlm.nih.gov/19162547/)].
- Pattanaik D, Lieberman JA. Pediatric angioedema. *Curr Allergy Asthma Rep*. 2017;**17**(9):60. doi: [10.1007/s11882-017-0729-7](https://doi.org/10.1007/s11882-017-0729-7). [PubMed: [28791569](https://pubmed.ncbi.nlm.nih.gov/28791569/)].
- Patel G, Pongracic JA. Hereditary and acquired angioedema. *Allergy Asthma Proc*. 2019;**40**(6):441–5. doi: [10.2500/aap.2019.40.4267](https://doi.org/10.2500/aap.2019.40.4267). [PubMed: [31690390](https://pubmed.ncbi.nlm.nih.gov/31690390/)].
- Byrd JB, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. *Immunol Allergy Clin North Am*. 2006;**26**(4):725–37. doi: [10.1016/j.iac.2006.08.001](https://doi.org/10.1016/j.iac.2006.08.001). [PubMed: [17085287](https://pubmed.ncbi.nlm.nih.gov/17085287/)].
- Volans A, Ferguson R. Using a bradykinin blocker in ACE inhibitor-associated angioedema in the emergency department. *BMJ Case Rep*. 2013;**2013**. doi: [10.1136/bcr-2012-008295](https://doi.org/10.1136/bcr-2012-008295). [PubMed: [23376672](https://pubmed.ncbi.nlm.nih.gov/23376672/)]. [PubMed Central: [PMC3603771](https://pubmed.ncbi.nlm.nih.gov/PMC3603771/)].
- Bartal C, Zeldetz V, Stavi V, Barski L. The role of icatibant-the B2 bradykinin receptor antagonist-in life-threatening laryngeal angioedema in the ED. *Am J Emerg Med*. 2015;**33**(3):479 e1–3. doi: [10.1016/j.ajem.2014.08.055](https://doi.org/10.1016/j.ajem.2014.08.055). [PubMed: [25241359](https://pubmed.ncbi.nlm.nih.gov/25241359/)].
- Hide M, Fukunaga A, Maehara J, Eto K, Hao J, Vardi M, et al. Efficacy, pharmacokinetics, and safety of icatibant for the treatment of Japanese patients with an acute attack of hereditary angioedema: A phase 3 open-label study. *Allergol Int*. 2020;**69**(2):268–73. doi: [10.1016/j.alit.2019.08.012](https://doi.org/10.1016/j.alit.2019.08.012). [PubMed: [31672405](https://pubmed.ncbi.nlm.nih.gov/31672405/)].
- Jeon J, Lee YJ, Lee SY. Effect of icatibant on angiotensin-converting enzyme inhibitor-induced angioedema: A meta-analysis of randomized controlled trials. *J Clin Pharm Ther*. 2019;**44**(5):685–92. doi: [10.1111/jcpt.12997](https://doi.org/10.1111/jcpt.12997). [PubMed: [31290163](https://pubmed.ncbi.nlm.nih.gov/31290163/)].
- Long BJ, Koyfman A, Gottlieb M. Evaluation and management of angioedema in the emergency department. *West J Emerg Med*. 2019;**20**(4):587–600. doi: [10.5811/westjem.2019.5.42650](https://doi.org/10.5811/westjem.2019.5.42650). [PubMed: [31316698](https://pubmed.ncbi.nlm.nih.gov/31316698/)]. [PubMed Central: [PMC6625683](https://pubmed.ncbi.nlm.nih.gov/PMC6625683/)].
- Zhou N, Wang L, Jiang J, Cheng P, Cui G, Wang F, et al. Application of ECMO successfully treated critically ill COVID-19 patients. *SSRN Electronic J*. 2020. doi: [10.2139/ssrn.3569889](https://doi.org/10.2139/ssrn.3569889).
- Cunningham AC, Goh HP, Koh D. Treatment of COVID-19: old tricks for new challenges. *Crit Care*. 2020;**24**(1):91. doi: [10.1186/s13054-020-2818-6](https://doi.org/10.1186/s13054-020-2818-6). [PubMed: [32178711](https://pubmed.ncbi.nlm.nih.gov/32178711/)]. [PubMed Central: [PMC7076992](https://pubmed.ncbi.nlm.nih.gov/PMC7076992/)].
- Pekdemir M, Ersel M, Aksay E, Yanturali S, Akturk A, Kiyan S. Effective treatment of hereditary angioedema with fresh frozen plasma in an emergency department. *J Emerg Med*. 2007;**33**(2):137–9. doi: [10.1016/j.jemermed.2007.02.024](https://doi.org/10.1016/j.jemermed.2007.02.024). [PubMed: [17692764](https://pubmed.ncbi.nlm.nih.gov/17692764/)].
- Katelaris CH. Acute management of hereditary angioedema attacks. *Immunol Allergy Clin North Am*. 2017;**37**(3):541–56. doi: [10.1016/j.iac.2017.04.002](https://doi.org/10.1016/j.iac.2017.04.002). [PubMed: [28687108](https://pubmed.ncbi.nlm.nih.gov/28687108/)].
- Bernstein JA, Qazi M. Ecallantide: its pharmacology, pharmacokinetics, clinical efficacy and tolerability. *Expert Rev Clin Immunol*. 2010;**6**(1):29–39. doi: [10.1586/eci.09.60](https://doi.org/10.1586/eci.09.60). [PubMed: [20383888](https://pubmed.ncbi.nlm.nih.gov/20383888/)].
- Depetri F, Tedeschi A, Cugno M. Angioedema and emergency medicine: From pathophysiology to diagnosis and treatment. *Eur J Intern Med*. 2019;**59**:8–13. doi: [10.1016/j.ejim.2018.09.004](https://doi.org/10.1016/j.ejim.2018.09.004). [PubMed: [30220453](https://pubmed.ncbi.nlm.nih.gov/30220453/)].
- Simon TL, Kalina U, Laske R, Mycroft S, Widmer E, Roth NJ. Manufacturing of plasma-derived C1-inhibitor concentrate for treatment of patients with hereditary angioedema. *Allergy Asthma Proc*. 2020;**41**(2):99–107. doi: [10.2500/aap.2020.41.190021](https://doi.org/10.2500/aap.2020.41.190021). [PubMed: [31796151](https://pubmed.ncbi.nlm.nih.gov/31796151/)].
- Kawasaki T, Chen W, Htwe YM, Tatsumi K, Dudek SM. DPP4 inhibition by sitagliptin attenuates LPS-induced lung injury in mice. *Am J Physiol Lung Cell Mol Physiol*. 2018;**315**(5):L834–45. doi: [10.1152/ajplung.00031.2018](https://doi.org/10.1152/ajplung.00031.2018). [PubMed: [30188745](https://pubmed.ncbi.nlm.nih.gov/30188745/)].