# Potential role of bradykinin and its receptors in COVID-19

## Potencjalna rola bradykininy i jej receptorów w COVID-19

Krystyna Obtułowicz[1], Paweł Dubiela[2,3], Kazimierz Madaliński[4], Wojciech Dyga[1], Piotr Obtułowicz[1]

[1] The Jagiellonian University, Medical College. University Hospital, HAE Center Krakow, Poland
[2] Department of Pathophysiology, Medical University of Vienna, Vienna, Austria
[3] Department of Regenerative Medicine and Immune Regulation, Medical University of Bialystok, Bialystok, Poland
[4] National Institute of Public Health - National Institute of Hygiene, Dept. Virology, Warsaw, Poland

**Summary**

Bradykinin (BK) is a nonapeptide that belongs to the kinin family. It is an active inflammatory mediator that exerts multiple different effects via its B1 and B2 receptors (B1R and B2R); however, its role has not been fully elucidated so far. It is known that B1R and B2R interact with angiotensin-converting enzyme (ACE)-2 protein, which acts as a receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19). By degrading BK to its desARG9-BK metabolite, ACE2 leads to B1R activation, which triggers a release of pro- and anti-inflammatory cytokines in an immune response to infectious pathogens. On the other hand, ACE2 stimulates the expression of B2R by activating the ANG(1-7)–MasR axis which is essential for proper endothelial function. A controlled increase in B1R-mediated cytokine release during SARS-CoV-2 cell entry may be considered a normal immune response aiming to prevent infection. However, if regulatory mechanisms fail, the increase in proinflammatory cytokine release may lead to progression of infection, endothelial activation, and onset of symptoms, including organ involvement. Available data strongly suggest that BK and its receptors are involved in the pathomechanism of COVID-19 and linked by various feedback mechanisms to ACE2, ACE1, as well as angiotensin II (ANGII) and its receptors. As expression of these pathways is likely to change dynamically throughout different stages of COVID-19, novel treatment options that target these pathways along with close monitoring of their activity should be developed.

**Keywords:** *ACE2, angiotensin II, bradykinin, COVID -19, crosstalk receptors*

**Streszczenie**

Bradykinina (BK) jest nonapeptydem należącym do rodziny kinin. Jest aktywnym mediatorem stanu zapalnego, który wywiera wiele różnych efektów poprzez swoje receptory B1 i B2 (B1R i B2R), jednak jej rola nie została do tej pory w pełni wyjaśniona. Wiadomo, że B1R i B2R oddziałują z białkiem konwertazy angiotensyny (ACE)-2, która działa jako receptor dla koronawirusa 2 (SARS-CoV-2), wywołującego chorobę COVID-19. Poprzez degradację BK do jego metabolitu desARG9-BK, ACE2 prowadzi do aktywacji B1R, co wyzwala uwalnianie cytokin pro- i przeciwzapalnych w odpowiedzi immunologicznej na patogeny. Z drugiej strony, ACE2 poprzez aktywację osi ANG(1-7)-MasR, stymuluje ekspresję B2R, która jest niezbędna dla prawidłowej funkcji śródbłonka. Kontrolowany wzrost uwalniania cytokin indukowany przez B1R podczas wnikania SARS-CoV-2 do komórek może być uznany za normalną odpowiedź immunologiczną zapobiegającą zakażeniu. Jeśli jednak mechanizmy regulacyjne zawiodą, wzrost uwalniania cytokin prozapalnych może prowadzić do progresji zakażenia, aktywacji śródbłonka i nasilenia objawów, w tym zajęcia narządów. Dostępne dane jednoznacznie sugerują, że BK i jego receptory są zaangażowane w patomechanizm COVID-19 i powiązane na drodze różnych mechanizmów sprzężenia zwrotnego z ACE2, ACE1, a także angiotensyną II (ANGII) i jej receptorami. Ponieważ ekspresja tych szlaków prawdopodobnie zmienia się dynamicznie w różnych stadiach COVID-19, należy opracować nowe opcje terapeutyczne ukierunkowane na te szlaki, ściśle monitorując ich aktywność.

**Słowa kluczowe:** *ACE2, angiotensyna II, bradykinina, COVID-19, receptory-krzyżowo zależne*



**Adres do korespondencji / Address for correspondence**
prof. Krystyna Obtułowicz MD PhD DSc
ul. Jagiellonska 9/5,
31-010 Krakow,
e-mail: mmobtulo@cyf-kr.edu.pl
phone 502 292 878,
fax 48 12 423 11 12

## Abbreviations:

**ACE** – angiotensin-converting enzyme
**ANGII** – angiotensin II
**BK** – bradykinin
**BR** – bradykinin receptor
**CAS** – contact activation system
**C1-INH** – **C1** inhibitor
**COVID-19** – coronavirus disease 2019
**DABK** – Des Arginin 9 Bradykinin

**ERDF** – endothelium-derived relaxing factor
**FVII** – coagulation factor VII
**FXII** – coagulation factor XII (Hageman Factor)
**IFN-γ** – interferon gamma
**IL** – interleukin
**KKS** – kallikrein kinin system
**NO** – nitric oxide
**PGI2** – prostacyclin
**RAAS** – renin-angiotensin-aldosterone system
**SARS-CoV-2** – severe acute respiratory syndrome coronavirus 2
**tPA**– tissue plasminogen activator

The course of the COVID-19 infection is various, changing, difficult to predict and ranges from asymptomatic to life-threatening conditions [1, 2, 3, 4, 5, 6, 7, 8, 9]. The majority of COVID-19 infections (in about 90% cases) are asymptomatic or manifest the mild symptoms (dry cough, fever, loss of sense of smell & taste, fatigue, myalgia, conjunctivitis). In the early mild symptoms phase – lasting usually 2-5 days - SARS-CoV-2 penetrates into the body and the asymptomatic patient can transmit the virus. This phase seems to be a period of unspecific/specific humoral and cellular immunity reaction which in majority of patients ends with full recovery. But about 20% of patients rapidly progress to severe illness (lasting 5-10 days) caused by infection of cells in the lower respiratory tract and develop bilateral pneumonia, acute respiratory distress syndrome and sometimes also multi-organ dysfunction [1, 10]. Patients who develop more severe forms of disease, present with high fever, dry cough and shortness of breath.

Laboratory studies show leukopenia, eosinopenia, neutrophilia, lymphopenia, elevated liver enzymes, increase of C-reactive protein, ferritin and hypokalemia as well as IL-2, IL-6 [1, 2, 5, 11, 12, 13, 14] and often reduced vitamin D3 level [15]. Some authors indicate the abnormal coagulation parameters [16, 17] as well as elevated activity of ANGII [6] in patients which after a few days of the mild symptoms phase progress to severe illness. Almost 10% of these critically ill patients die. Autopsies and histological analysis indicate extensive hyaline membrane in the exudative phase of diffuse alveolar damage [1, 7, 18, 19, 20, 21, 22, 23], pneumonitis with disruption of the epithelial-endothelial barrier, diffuse alveolar damage with severe capillary congestion and various findings of lungs and other organs suggesting vascular dysfunction, endothelial damage, complement deposition, blood clotting, systemic microangiopathy indicating on the immune hyperreactivity [1, 7, 10, 18].

Bradykinin (BK) is a nonapeptide that belongs to the kinin family. Similar to angiotensin (ANG) and histamine, it is an active tissue hormone (autacoid) with various functions (Fig. 1) [24, 25, 26, 27, 28, 29]. However, its role is underestimated [28] and has not been fully elucidated so far. Bradykinin is an inflammatory mediator and a major endogenous regulator of endothelial function [26, 30]. It is known to reduce blood pressure due to its vasodilatory action, to increase capillary permeability, as well as to induce local angioedema, cough, and neuropathic pain [26, 27, 28, 30, 31].

Bradykinin is produced by kallikrein from high and low-molecular-weight kininogens. Its plasma proenzyme, bradykininogen, is converted to lysyl-bradykinin by the action of locally released tissue kallikrein and then to an active short-lived bradykinin metabolites (Fig. 2) by an angiotensin-converting enzymes: ACE 1 and 2 (Table 1 and Fig. 3) [1, 25, 26, 32], whose activities can be regulated by ACE inhibitors and angiotensin receptor blockers.

Bradykinin production is increased under the influence of FXII, FVII, complement activation, plasmin [33, 34, 35] and many others substances as mast cell tryptase and mast cell heparin. The main inhibitor of its production is C1 inhibitor [25, 26, 29]. Bradykinin exerts its effects mainly via its $B_2$

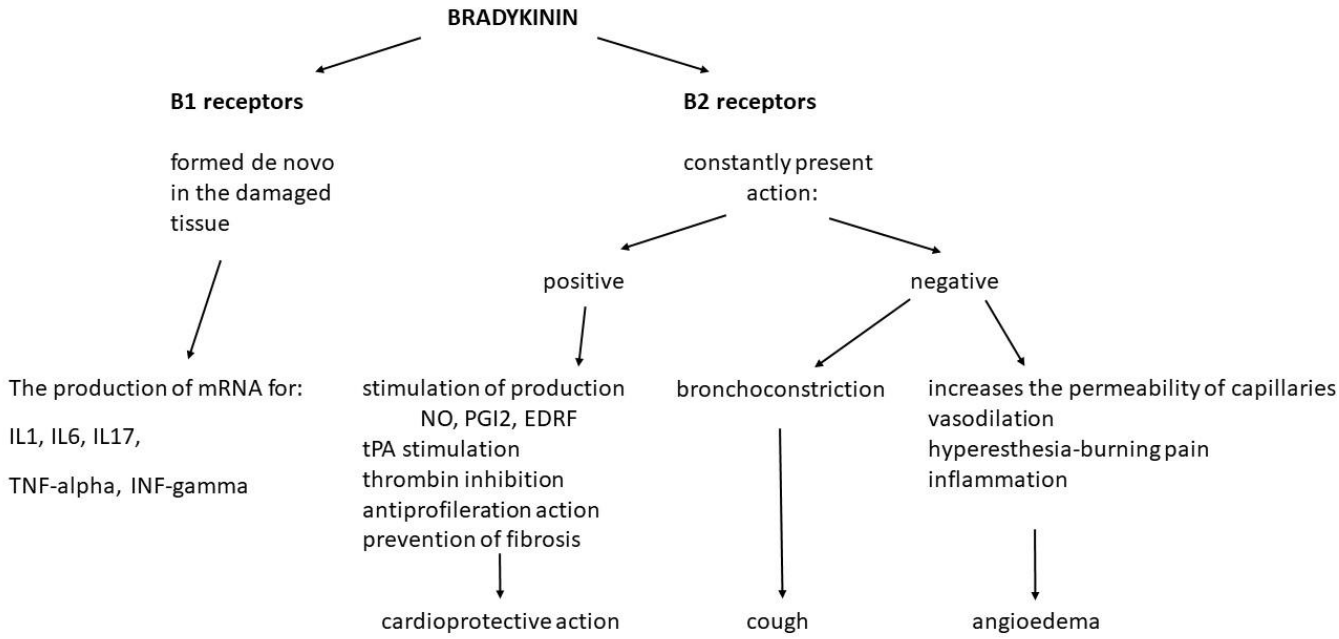


Fig 1: Bradykinin receptors action
Abbreviations: tPA - tissue plasminogen activator, PGI2 - prostacyclin; EDRF- endothelium-derived vascular relaxing factor.

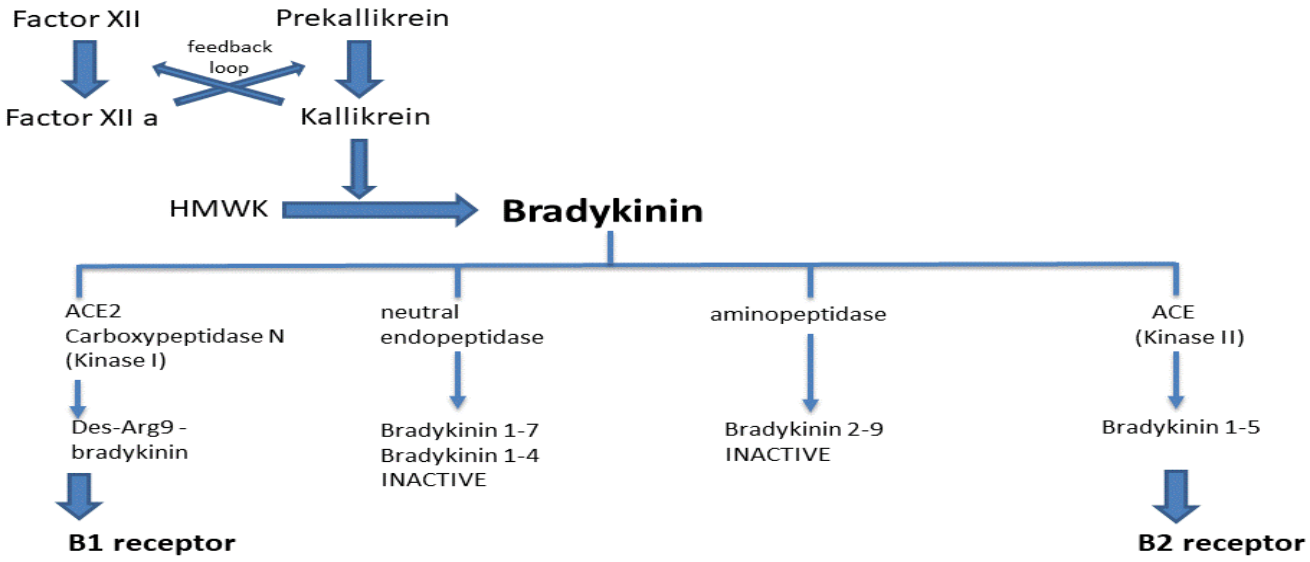


Fig 2 Bradykinin production and degradation

Abbreviations: ACE 1 (kinase II, angiotensin-converting enzyme), ACE 2 (kinase I, carbocypeptidase N ), HMWK - high-molecular-weight kininogen.

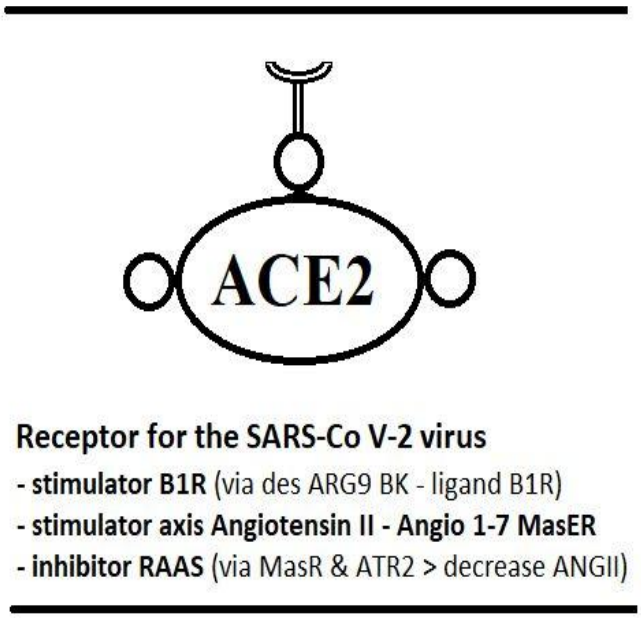


Fig 3. ACE2 (carboxypeptydase N, kinase I)

and $B_1$ receptors [26, 27, 29,31, 32]. They are in constant cooperation with each other and with receptors of other systems, as angiotensin receptors, as well as with ACE2 and 1 (Fig. 3 and 4) [12, 13, 14,16, 37, 38, 39, 40]. $B_2$ receptors (B2R), are constitutively expressed and $B_1$ receptors (B1R), are activated *de novo* only in response to inflammation or tissue injury (Fig. 1) [26, 27, 31]. B2R receptors regulate the synthesis of inflammation mediators with opposite functions (Fig. 1). The first are mediators with a protective effect on endothelium, such as prostacyclin (PGI2), nitric oxide (NO), endothelium-derived relaxing factor (EDRF), tissue plasminogen activator (tPA). These mediators reveal also antithrombotic, antifibrotic and antiproliferative effects [26, 41, 42, 43, 44, 45]. To the second group of negative mediators B2R (Fig.1) belong these promoting so-called bradykinin-induced cough reduced by B2R antagonist and acute bradykinin pain as well as symptoms associated with burning mouth syndrome [26, 28] and mediators which induce vasodilation and capillar leakage observed in histopathological studies in severe symptoms phase in patients with COVID-19 [17, 20, 21, 22, 23, 47].

The activation of B1R in COVID-19 patients is potentially associated with the natural immune response to the entry of the virus. This reaction manifests itself in production of interferon gamma (INF-$\gamma$), pro-and anti-inflammatory cytokines involved in specific and nonspecific immune response (Fig. 4) [1, 11, 48, 49, 50, 51, 52, 53].

It appears that in patients with COVID-19 infection together with the illness progress in severe symptoms phase compared to the asymptomatic phase [54] we are dealing with chaotic complex immune dysregulation [55] connected with cytokine [1, 10, 11, 49, 50, 51, 52, 53, 56] bradykinin [1, 32, 56, 57, 58, 59] and may be also hyaluronian storm [1, 16, 19, 23], as well as chaotic activation of the complement system and fibrinolysis [34, 35] which leads to hyperinflammation, vasculitis as well as hypercoagulation [1, 37, 38, 60, 61 62] similar to that found in bradykinin angioedema due to C1-INH deficiency [25, 29, 63].

Considering given facts, we hypothesize two variants that correspond with severity of COVID-19 infection. Activation of B1R influenced by the increase of DABK occurs already in the initial, usually asymptomatic phase of COVID-19 [1, 10, 11, 26, 52, 54, 64] and is related to natural defense reaction of the immune system, with increase of IFNs as well as other pro- and anti-inflammatory cytokines. If activation is under control the patient recovers. Otherwise, when viremia is enhanced, there may be excessive activation of B1R and thus an increase in proinflammatory cytokines, especially harmful to endothelium IL-6 [1, 42, 44, 56, 57, 65, 66]. This, in turn, results in development of various organ complications observed in patients suffering from COVID-19 with a severe phenotype.

B2Rs are very active receptors involved in many processes and closely cooperating with B1R and many other systems receptors (Fig. 4) [1, 26, 67]. Their activation can have bidirectional effect on the systemic reactions. Physiological

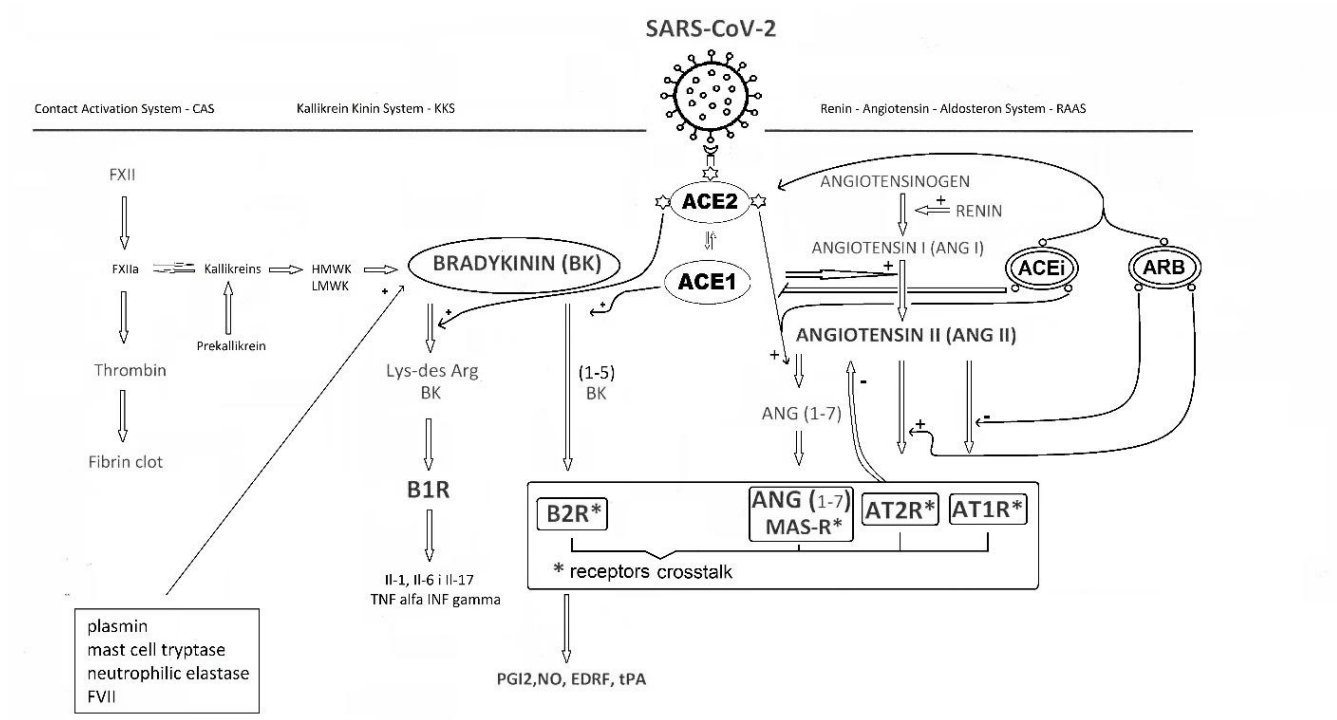


Fig 4 ACE2 in pathomechanism of COVID-19

Abbreviations:

ACE1 – kinase II, angiotensin coverting enzyme 1

ACE2 – kinase I, carbocypeptidase N

HMWK – high molecular weight kininogen

LMWK – low molecular weight kininongen

ACEi – angiotensin coverting enzyme inhibitor

ARB – angiotensin receptor blocker

ATR1 – angiotensin II receptor 1

ATR2 – angiotensin II receptor 2

MASR – angiotensin 1 -7 receptor

B1R – Bradykinin receptor 1

B2R – Bradykinin receptor 2

Table I. Properties of angiotensin-converting enzymes (ACE2 & ACE1)

| Enzyme type | Properties |
|---|---|
| ACE2 | **SARS–CoV-2 receptor** |
| | metabolizes bradykinin to Des Arg9 BK (DABK)<br>cleaves ANGI to ANG(1-7), ANG(1-9) |
| | stimulates B1R via DABK-ligand B1R |
| | stimulates axis ANG(1-7)-MasR- |
| ACE 1 | metabolizes bradykinin mainly to BK1-5 |
| | cleaves ANGI to ANGII acting through the AT1R |

ACE 1 < feedback loop > ACE 2

ACE 1 and 2 act as a counter balance for RAAS

Table II. Properties of angiotensin-converting enzyme (ACEi) inhibitors and angiotensin receptor blockers (ARB)

| |
|---|
| **ACEi :** |
| Inhibit ACE1 |
| Increase ACE2 expression |
| Increase BK level via blocking its metabolism |
| Activate B2R via stimulation of the ANGII-ANG(1-7)-MasR axis – B2R |
| **ARB:** |
| Inhibit AT1R > reduction of ANGII |
| Increase ACE2 expression |
| Activate ACE2 |
| Activate the ANG(1-7)-MasR axis |
| Suppress inflammatory cytokine release (TNF-α, IFN-γ, IL-1β, and IL-6) |
| Increase the expression of anti-inflammatory cytokine IL-10 |

**Abbreviations:** ACE – angiotensin-converting enzyme; ACEi – angiotensin-converting enzyme inhibitor; ANG – angiotensin, ARB – angiotensin receptor blocker; AT1R – angiotensin II receptor type 1; BK – bradykinin; IFN-γ – interferon γ; IL– interleukin; TNF-α – tumor necrosis factor α.

activation of B2R is related to the induction of endothelium protective mediators such as NO, PGI2, EDRF (Fig. 1) and cardioprotective action [26, 30, 42]. Hyperactivity and dysregulation of these receptors, that occurs in the course of various disease processes, can lead to cough and pain as well as olfactory and taste disorders often present in patients already in the early stage of COVID-19 infection. B2R are also responsible for endothelium injury, increased capillary permeability, vasodilation, coagulopathy, angioedema [25, 26, 68, 69,70].

Coming to BK, it is worthy to highlight its role as a natural antioxidant involved in maintaining homeostasis [72, 73]. It regulates the redox balance in a human body by feedback interactions (Fig. 4) with numerous cascade systems, such as RAAS, CAS, coagulation, fibrinolysis and complement systems [1, 26, 62, 70, 74, 75, 76, 77, 78, 79].

To play such a role it has a special biochemical feature namely, a very short half-life [24, 25, 26]. Its metabolism and inactivation are regulated by 4 peptidases (Fig. 2) [1, 26]. The main peptidase that catalyzes BK into its metabolites (mainly to BK1-5) which stimulate B2R is ACE1 – kinase II. (Fig. 4). However, ACE2 – kinase I (carboaminopeptidase N), presently known as a receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [80, 81, 82, 83, 84, 85] is the only one of these 4 peptidases that metabolizes BK to desArg$^{9}$BK (DABK), which acts as a ligand for B1R. It strictly show that further researches are needed to fully clarify interplay especially by BK, ACE1/2 and RAAS.

## In conclusion:

1. BK and its receptors, B1R and B2R, seem to play a significant role in the pathomechanism of COVID-19. The changes in their activity depending on the stage and severity of COVID-19 infection aim to preserve homeostasis.
2. Activation and dysregulation of B1R in COVID-19 by ACE 2 via DABK is an important antiviral natural defensive reaction which induces pro- and anti-inflammatory cytokines release leading to hyperinflammatory reactions and especially to endothelium inflammation and vasculitis.
3. Activation and dysregulation of B2R via ANG(1-7)-MasR axis triggered by ACE2, which causes increased levels of cardioprotective mediators (PGI2, NO, EDRF) in an early stage of infection, is protective for endothelium. While its overexpression in a severe stage of COVID-19 enhances severity of the symptoms (vasodilation, hyperinflammation, coagulopathy and vasculitis).
4. Although not fully elucidated, it is speculated that the complex and dynamically changing immune environment during COVID-19 involves other molecules of humoral immunity as complement and plasmin systems.

We believe that without fully understanding the role of bradykinin, its receptors and monitoring of important inflammatory mediators in COVID-19 infection, we will not be able to program effective treatment, especially in severe cases [86]. As the pandemy is a major health burden of the 21$^{st}$ century so far, we feel obliged to perform further studies to solve this complicated dilemma.

## References


1. Garvin MR, Alvarez Ch, Miller JI, Prates ET, Walker AM, Amos BK, Mast AE, Justice A, Aronow B, Jacobson D. A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bradykinin storm. eLife. 2020; 9: e59177. Published online 2020 Jul 7. doi: 10.7554/eLife.59177
2. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, Satlin MJ, Campion TR, Nahid M, Ringel JB, Hoffman KL, Alshak MN, Li HA, Wehmeyer GT, Rajan M, Reshetnyak E, Hupert N, Horn EM, Martinez FJ, Gulick RM, Safford MM. Clinical characteristics of Covid-19 in New York city. New England Journal of Medicine. 2020;382:2372–2374. doi: 10.1056/NEJMc2010419.
3. Patel R, Babady E, Theel ES, et al. Report from the American Society for Microbiology COVID-19 International Summit, 23 March 2020: Value of Diagnostic Testing for SARS-CoV-2/COVID-19. mBio. 2020;11(2):e00722-20. doi: 10.1128/mBio.00722-20.
4. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19) JAMA Cardiology. 2020; 27:e201017. doi: 10.1001/jamacardio.2020.1017.
5. Li H, Liu L, Zhang D, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. Lancet. 2020 May 9;395(10235):1517-1520. doi: 10.1016/S0140-6736(20)30920-X
6. Reddy R, Asante I, Liu S, et al. Circulating angiotensin peptides levels in Acute Respiratory Distress Syndrome correlate with clinical outcomes: a pilot study. PLoS One. 2019; 14: e0213096.https://doi.org/10.1371/journal.pone.0213096
7. Menter T, Haslbauer JD, Nienhold R, Savic S, Hopfer H, Deigendesch N, et al. Post-mortem examination of Covid-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings of lungs and other organs suggesting vascular dysfunction. Histopathology. 2020; +77(2): 198-209.https://doi.org/10.1111/his.14134
8. Lai C.-C. Shih T.-P. Ko W.-C. Tang H.-J. Hsueh P.-R. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020; (2020/02/17/)105924
9. Peiro C, Moncada S. Substituting angiotensin-(1-7) to prevent lung damage in SARSCoV2 infection? Circulation 2020;141(21):1665-1666.doi: 10.1161/CIRCULATIONAHA.120.047297.
10. Perico L, Benigni A, Casiraghi F, Ng LFP, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nat Rev Nephrol. 2020 Oct 19: 1–19. doi: 10.1038/s41581-020-00357-4
11. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19 J of Infection 2020, 80, (6) P607-613, https://doi.org/10.1016/j.jinf.2020.03.03
12. Herold T, Jurinovic V, PhD, Arnreich Ch, Hellmuth JC, von Bergwelt-Baildon M, Klein M, and Weinberger T. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19 J Allergy Clin Immunol. 2020;146(1):128–136.e4. Published online 2020 May 18. doi: 10.1016/j.jaci.2020.05.008
13. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, Mucheli SS, Kuperan P, Ong KH. Hematologic parameters in patients with COVID-19 infection. American Journal of Hematology. 2020; 95:E131–E134. doi: 10.1002/ajh.25774.
14. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020; 55: 102763. doi: 10.1016/j.ebiom.2020.102763
15. Grant WB, Lahore H, McDonnell ML et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 2020, 12, 988.https://www.mdpi.com/2072-6643/12/4/988
16. Mustafa A, McKallip RJ, Fisher M, Duncan R, Nagarkatti PS, Nagarkatti M. Regulation of interleukin-2-induced vascular leak syndrome by targeting CD44 using hyaluronic acid and anti-CD44 antibodies. Journal of Immunotherapy.2002; 25:476–488. doi: 10.1097/00002371-200211000-00004.
17. Polidoro RB , Hagan RS, de Santis Santiago R and Schmidt NW. Overview :Systemic Inflammatory Response Derived From Lung Inmjury Caused by SARS-Co-V-2 Infection Explains Severe Outcomes in COVID 19. Front. Immunol., 26 June 2020. . https://doi.org/10.3389/fimmu2020.01626
18. Thomson TM, Toscano E, Casis E, Paciucci R. C1 esterase inhibitor and the contact system in COVID-19. Br J Haematol. 2020; 190(4): 520-524. /doi.org/10.1111/bjh.16938.
19. Han SW, Park MJ, Lee SH. Hyaluronic acid-induced diffuse alveolar hemorrhage: unknown complication induced by a well-known injectable agent. Ann Transl Med . 2019 Jan;7(1):13. doi: 10.21037/atm.2018.11.51.
20. Barton LM, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S. COVID-19 autopsies, Oklahoma, USA. American Journal of Clinical Pathology. 2020;153:725–733. doi: 10.1093/ajcp/aqaa062.
21. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang Ch et al. Pathological findings of COVID-19 associated with acute respiratory distress syndromeLancet Respir Med. 2020;8(4): 420–422. Published online 2020 Feb 18. doi: 10.1016/S2213-2600(20)30076-X,
22. Adachi T, Chong J-M, Nakajima N, et al Clinicopathologic and immunohistochemical findings from autopsy of patient with COVID-19, Japan. Emerging Infectious Diseases. 2020;26:201353. doi: 10.3201/eid2609.201353.
23. Mong MA, Awkal JA, Marik PE. Accelerated hyaluronan concentration as the primary driver of morbidity and mortality in high-risk COVID-19 patients: with therapeutic introduction of an oral hyaluronan inhibitor in the prevention of 'Induced Hyaluronan Storm' Syndrome. medRxiv. 2020; April 30, doi: 10.1101/2020.04.19.20071647.
24. Nussberger J, Cugno M, Cicardi M. Bradykinin-mediated angioedema. New Engl J Med. 2002; 347: 621-622.
25. Kaplan AP, Joseph K. Pathogenic mechanisms of bradykinin mediated diseases:dysregulation of an innate inflammatory pathway. Adv Immunol 2014;121:41-89.
26. Obtulowicz K. Bradykinin mediated angioedema. Pol Arch Intern Med. 2016; 126: 76-85. DOI: 10.20452/pamw.3273
27. Hofman Z, de Maat S, Hack CE, Maas C. Bradykinin: inflammatory product of the coagulation system. Clinical Reviews in Allergy & Immunology. 2016;51:152–161. doi: 10.1007/s12016-016-8540-0.
28. Belowska-Bień K, Szeląg E, Szeląg J, Skrzypiec-Spring M. Bradykinin – an undervalued mediator? Post N Med. 2017; 440-446.
29. Cicardi M, Zuraw BL. Angioedema due to bradykinin dysregulation. J Allergy Clin Immunol Pract. 2018; 6: 1132-1141.
30. Gryglewski RJ, Uracz W, Chłopicki S, Marcinkiewicz E. Bradykinin as a major endogenous regulator of endothelial function. Pediatr Pathol Mol Med. 2002; 21: 279-290.
31. Bas M, Adams V, Suvorava T, et al. Nonallergic angioedema: role of bradykinin. Allergy. 2007; 62: 842-856.
32. Sodhi Ch P , Wohlford-Lenane Ch, Yamaguchi Y, Prindle Th, Fulton WB, Wang S, McCray Jr PB, Chappell P , Hackam DJ, Jia H. 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 Jan 1;314(1):L17-L31. doi:0.1152/ajplung.00498.2016.
33. Maas C. Plasminflammation-An Emerging Pathway to Bradykinin Production. Front Immunol. 2019 Aug 27;10:2046. doi: 10.3389/fimmu.2019.02046.

34. Ji HL, Zhao R, Matalon S, Matthay MA. Elevated plasmin(ogen) as a common risk factor for COVID-19 susceptibility. Physiol Rev. 2020; 100: 1065-1075. Published online 2020 Mar 27. doi: 10.1152/physrev.00013.2020
35. Cugno M, Meroni PL, Gualtierotti R, Griffini S, Grovetti E, Torri A, et al. . Complement activation in patients with Covid-19: A novel therapeutic target. J Allergy Clin Immunol. 2020 Jul; 146(1): 215–217. Published online 2020 May 14. doi: 10.1016/j.jaci.2020.05.006
36. Dyga W, Obtułowicz A, Bogdali A, Mikolajczyk T, Czarnobilska E, Obtułowicz K. Expression of bradykinin receptors on PBMC collected from patients with HAE and chronic spontaneous urticarial. Bradykinin Symposium Abstracts, Berlin 5-6 September 2018 : 16, OP.07. www.bradykinin-symposium.de
37. Rasaeifar B, Gomez-Gutierrez P, Perez JJ. Molecular Features of Non-Selective Small Molecule Antagonists of the Bradykinin Receptors. Pharmaceuticals (Basel) 2020; 3(9):259. doi: 10.3390/ph13090259.
38. Bai F, Pang XF, Zhang LH, Wang NP, McKallip RJ, Garner RE, Zhao ZQ. Angiotensin II AT1 receptor alters ACE2 activity, eNOS expression and CD44-hyaluronan interaction in rats with hypertension and myocardial fibrosis. Life Sciences. 2016;153:141–152. doi: 10.1016/j.lfs.2016.04.013.
39. Mogielnicki A, Kramkowski K, Hermanowicz JM, Leszczynska A, Przyborowski K, Buczko W. Angiotensin-(1-9) enhances stasis-induced venous thrombosis in the rat because of the impairment of fibrinolysis. Journal of the Renin-Angiotensin-Aldosterone System. 2014;15:13–21. doi: 10.1177/1470320313498631.
40. Cerrato BD, Carretero OA, Janic B, et al. Heteromerization between the bradykinin B2 receptor and the angiotensin-(1-7) Mas receptor: functional consequences. Hypertension. 2016; 68:1039-1048. https://doi.org/10.1161/HYPERTENSIONAHA.116.07874
41. Tang N., Li D., Wang X., Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemostasis. 2020;18:844–847.
42. Lau J, Rousseau J, Kwon D, Bernard F, Link KS. A Systematic Review of Molecular Imaging Agents Targeting Bradykinin B1 and B2 Receptors .Pharmaceuticals 2020, 13(8), 199-201.
43. Dutra RC, Bento AF, Leite DF, et al. The role of kinin B1 and B2 receptors in the persistent pain induced by experimental autoimmune encephalomyelitis (EAE) in mice: evidence for the involvement of astrocytes. Neurobiol Dis. 2013; 54: 82-93.
44. Couture R, Blaes N, Girolami JP. Kinin receptors in vascular biology and pathology. Curr Vasc Pharmacol. 2014; 12: 223-248.
45. Schmaier AH. The contact activation and kallikrein/kinin systems: pathophysiologic and physiologic activities. Journal of Thrombosis and Haemostasis. 2016;14:28–39. doi: 10.1111/jth.13194.
46. Dorris SL, Peebles RS Jr. PGI2 as a regulator of inflammatory diseases. Mediators Inflamm. 2012; 12: 926-968
47. Pernazza A, Mancini M, Rullo E, Bassi M, De Giacomo T, Della Rocca C, d'Amati G. Early histologic findings of pulmonary SARS-CoV-2 infection detected in a surgical specimen Virchows Arch 2020; 77(5):743-748. doi: 10.1007/s00428-020-02829-1.
48. Gieryńska M, Schollenberger M. Molecular recognition of viral infections – immune response stimulation. Post Hig Med Dośw (Online). 2011; 65: 299-313.
49. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes & immunosuppression. Lancet. 2020; 395: 1033-1034.
50. van de Veerdonk, F.; Netea, M.G.; van Deuren, M.; van der Meer, J.W.; de Mast, Q.; Bruggemann, R.J.; van der Hoeven H. Kinins and Cytokines in COVID-19: A Comprehensive Pathophysiological Approach. Preprints 2020, 2020040023 (doi: 10.20944/preprints202004.0023.v1).
51. Schmidt ME, Varga SM. Cytokines and CD8 T cell immunity during respiratory syncytial virus infection. Cytokine 2020; Sep;133:154481. doi: 10.1016/j.cyto.2018.07.012.
52. Mahmudpour M, Roozbeh J, Keshavarz M, Farrokhi S, Nabipour COVID-19 cytokine storm: The anger of inflammation. I. Cytokine. 2020 Sep;133:155151. doi: 10.1016/j.cyto.2020.155151.
53. Zuccari S. Damiani E. Domizi R. Scorcella C. D'Arezzo M. Carsetti A. et al. Changes in cytokines, haemodynamics and microcirculation in patients with sepsis/septic shock undergoing continuous renal replacement therapy and blood purification with cytoSorb. Blood Purificat. 2020; 49: 107-113
54. Long Q-X, Tang X-J, Shi Q-L, Li Q, Deng H-J, Yuan J, Hu J-L, Xu W, Zhang Y, Lv F-J, Su K, Zhang F, Gong J, Wu B, Liu X-M, Li J-J, Qiu J-F, Chen J, Huang A-L. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nature Medicine. 2020;63:6. doi: 10.1038/s41591-020-0965-6.
55. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, et al. . Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe. 2020; 27(6):992–10007. doi: 10.1016/j.chom.2020.04.009. Epub 2020 Apr 21.
56. Teijaro J.R. Walsh K.B. Cahalan S. Fremgen D.M. Roberts E. Scott F. et al.Endothelial cells are central orchestrators of cytokine amplification during influenza virus infection.Cell. 2011; 146: 980-991 doi: 10.1016/j.cell.2011.08.015.
57. Taylor SL, Wahl-Jensen V, Copeland AM, et al. Endothelial cell permeability during hantavirus infection involves factor XII-dependent increased activation of the kallikrein-kinin system. Res Pract Thromb Haemost. 2020; 4: 205-216. doi: 10.1371/journal.ppat.1003470.57.
58. Ghahestani SM, Mahmoudi J, Hajebrahimi S, 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: 13-17.
59. Meini S, Zanichelli A, Sbrojavacca R, Juri F, Roberts AT, Suffriti Ch and Tascini C.Understanding the Pathophysiology of COVID-19:Could the Contact System Be the Key ? Front Immunol 2020;August 11, https://doi.org/10.3389/fimmu.2020.02014
60. van de Veerdonk FL, Netea MG,van Deuren M,et al. Kallikrein-kinin blockade in patients with COVID-19 to prevent acute respiratory distress syndrome. eLife 2020;9:e57555 doi: 10.7554/eLife.57555
61. Danser AHJ, Epstein M, Batlle D. Renin-angiotensin system blockers and the COVID-19 pandemic: at present there is no evidence to abandon renin-angiotensin system blockers. Hypertension. 2020; 75: 1382-1385.
62. Levi M. Thachil J. Coronavirus Disease 2019 Coagulopathy: Disseminated Intravascular Coagulation and Thrombotic Microangiopathy—Either, Neither, or Both. Semin Thromb Hemost. 2020 Oct; 46(7): 781–784. Published online 2020 Jun 8. doi: 10.1055/s-0040-1712156
63. Obtułowicz K, Dyga, Natorska J, et al. Elevated thrombin generation and factor VIII activity during angioedema attack in patients with hereditary C1 inhibitor deficiency. Pol Arch Intern Med. 2019; 129(12): 936-938.doi:10.20452/pamw.15096
64. Datta PK, Liu F, Fischer T, Rappaport J, Qin X. SARS-CoV-2 pandemic an research gaps: Understanding SARS-CoV-2 interaction with the ACE2 receptor and implications for therapy. Theranostics. 2020 Jun 12;10(16):7448-7464. doi: 10.7150/thno.48076.
65. Weissenberger CA, Stetter C, Meuth SG, Göbel K, Bader M, Sirén, Kleinschnitz C. Blocking of bradykinin receptor B1 protects from focal closed head injury in mice by reducing axonal damage and astroglia activation. J. Cereb. Blood Flow Metab 2012; 32 (9):1747-1756. .
66. Magro C, J, Mulvey JJ, Berlin D, Nuovo G,Salvatore S, Harp J, Baxter-Stoltzfus A, Laurence J.. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases Transl Res 2020; 220:1-13. doi: 10.1016/j.trsl.2020.04.007.

67. Blaes N, Girolami JP. Targeting the 'Janus face' of the B2-bradykinin receptor. Expert Opin Ther Targets. 2013; 17: 1145-1166. doi: 10.1517/14728222.2013.827664.
68. Koyama K, Katayama S, Tonai K, et al. Biomarker profiles of coagulopathy and alveolar epithelial injury in acute respiratory distress syndrome with idiopathic/immune-related disease or common direct risk factors. Crit Care 2019; 23: 283.
69. O'Sullivan J M, Mc Gonagle D,Ward SE,Preston RJS, O'Donnell JS. Endothelial cells orchestrate COVID-19 coagulopathy. The Lancet Haematology 2020; 7(8): 553-555 DOI: 10.1016/s2352-3026(20)30215-5
70. Levi M, Toshiaki JT, Iba I, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19 The Lancet Hematology. 2020; 7(6), 438-e440. DOI:https://doi.org/10.1016/S2352-3026(20)30145-9
71. Zwaveling S, van Wijk RG, Karim F.Pulmonary edema in COVID-19: Explained by bradykinin? JACI 2020; DOI:https://doi.org/10.1016/j.jaci.2020.08.038
72. Firinu D, Costanzo GAML, Del Giacco SR. Oxidative stress in hereditary angioedema caused by C1 inhibitor deficiency: an interesting finding that deserves further studies. Pol Arch Intern Med. 2020; 130: 73-75. doi: 10.20452/pamw.15213
73. Obtułowicz K, Góralska J, Bogdali A, et al. Bradykinin and oxidative stress in patients with hereditary angioedema due to C1 inhibitor deficiency. Pol Arch Intern Med. 2020; 130: 79-88. doi:10.20452/pamw.15138
74. Bossi F, Bulla R. New emerging roles for complement and kinin systems in angioedema episodes associated with C1 inhibitor deficiency. J Angioedema. 2011; 1: 13-18.
75. Urwyler P, Moser P, M.. Treatment of COVID-19 With Conestat Alfa, a Regulator of the Complement, Contact Activation and Kallikrein-Kinin System Front Immunol . 2020 Aug 14;11:2072. doi: 10.3389/fimmu.2020.02072.
76. Erdös EG, Jackman HL, Brovkovych V, Tan F, Deddish PA. Products of angiotensin I hydrolysis by human cardiac enzymes potentiate bradykinin. Journal of Molecular and Cellular Cardiology. 2002;34:1569–1576. doi: 10.1006/jmcc.2002.2080.
77. Qadri F, Bader M. Kinin B1 receptors as a therapeutic target for inflammation. Expert Opinion Therapeutic Targets 2018;22 (1):31-44.
78. Schmaier AH. The plasma kallikrein-kinin system counterbalances the renin-angiotensin system. Journal of Clinical Investigation. 2002;109:1007–1009. doi: 10.1172/JCI0215490.
79. Risitano AM , Complement as a target in COVID-19?Nature Reviews Immunology2020; 20:343–344.
80. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003; 426: 450-454. https://doi.org/10.1038/nature02145.
81. Zisman LS. ACE and ACE2: a tale of two enzymes. Eur Heart J. 2005; 26 (4): 322-4. doi: 10.1093/eurheartj/ehi043.
82. Walls AC, Park YJ, Tortorici MA, et al. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020; 181(2): 281-292.e6. doi: 10.1016/j.cell.2020.02.058
83. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 181(2): 271-280.e8.doi: 10.1016/j.cell.2020.02.052.
84. Ingraham NE, Barakat AG, Reilkoff R, Bezdicek T, Schacker T, Chipman J G, Tignanellis ChJ and Puskarich MA. Understanding the renin-angiotensin-aldosterone-SARS-CoV axis: a comprehensive review. Eur Respir J 2020;56:2000912[https://doi.org/10.1183/13993003.00912-2020.
85. Chen J, Jiang Q, Xia X, et al. Individual variation of the SARS-CoV2 receptor ACE2 gene expression and regulation. Aging Cell 2020; 19(7):e13168. doi: 10.1111/acel.13168.
86. Dixon DL, Van Tassell BW, Vecchié A, et al. Considerations in Treating Patients With Coronavirus Disease 2019 (COVID-19) J Cardiovasc Pharmacol . 2020 May;75(5):359-367.