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REVIEW ARTICLE

Vasoactive Peptides: Role in COVID-19 Pathogenesis and Potential Use as Biomarkers and Therapeutic Targets

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Background. The ongoing outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as the latest threat to global health, causes overwhelming effects for the public healthcare systems worldwide. Of note, in addition to the respiratory complications, some patients with coronavirus disease 2019 (COVID-19) also develop serious cardiovascular injuries. Vasoactive peptides play an important role in a wide range of physiological and pathological conditions.

Aim. With the urgent need for exploring the specific therapeutic targets and biomarkers for the emerging COVID-19, the general aim of this review is to discuss the potentials of the vasoactive peptides including Angiotensin II (Ang II), vasoactive intestinal peptide (VIP), endothelin-1 (ET-1), calcitonin gene-related peptide (CGRP), natriuretic peptides, substance P (SP) and bradykinin (BK) as therapeutic targets and/or prognostic indicators for the COVID-19 pandemic.

Conclusion. Based on various observations some authors conclude that the assessment of vasoactive peptides shall be considered a routine part of COVID-19 patient monitoring, and they can serve as potential therapeutic targets for the disease management.

KeyWords: COVID-19, SARS-CoV-2, Vasoactive peptides, Angiotensin II.

Introduction

The coronavirus disease 2019 or COVID-19, is a novel infectious disease that was first identified as pneumonia of unknown cause in Wuhan city in December 2019 (1). Following the rapid spreading of the virus worldwide, the World Health Organization (WHO) on 30th January 2020 declared that COVID-19 as the sixth public health emergency of international concern (2). At the end of March 2021, the COVID-19 is affecting 219 countries and territories worldwide, leading to more than 127 million infected cases have been detected as well as killed approximately 2.8 million patients (3). The coronavirus was officially renamed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses according to phylogenetic analysis (4).

The clinical features range from an asymptomatic state to severe acute respiratory failure and multi-organ dysfunction. The common clinical symptoms are fever, dry cough, anosmia, sore throat, shortness of breath, fatigue, headache, and myalgia (5). Furthermore, multi-organ dysfunctions such as cardiovascular complications, renal failure, gastrointestinal symptoms, hematological symptoms, neurological manifestations, in some patients with COVID-19 have been reported (6).

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Entrance into host cells is considered the first stage in viral infection. Zhou and colleagues demonstrated that angiotensin-converting enzyme 2 (ACE2) expressed on the cell surface provides the gate to entry for SARS-CoV-2 into host cells and for this type of coronavirus, there is no need for another receptors, such as aminopeptidase N (APN) and dipeptidyl peptidase 4 (DPP4), which serve as the entry receptors for other human coronaviruses, namely HCoV-229E and MERS-CoV (7). Thus, ACE2 plays a decisive role as a functional receptor for viral spikes of SARS-CoV-2 (8). The SARS-CoV-2 spike (S) glycoprotein plays a critical role in binding to the receptor, membrane fusion, and internalization (9). In brief, during viral infection, the receptor-binding domain (RBD) of the s glycoprotein binds to the region located in the peptidase domain of ACE2. Membrane fusion of the virus and the host cell activate and eventually viral RNA is released into the cytoplasm, leading create infection (10). It has been shown that the ACE2 protein express in varying degrees in almost all human organs and tissues, including respiratory mucosa, lung, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, bladder urothelial cells, and nervous system (11). On the other hand, cell-free and macrophage-phagocytosed viruses may be conveyed to other tissues and lead to infection in ACE2-expressing cells at local sites via blood circulation (10).

Currently, despite the identification of available targets for treatment, there is still no definitive treatment for infected patients. The COVID19 treatment mostly is based on patients' symptoms and there are no specific antiviral agents suggested for SARS-CoV-2 (12). There are some targets to inhibit viral prevalence, for example, SARS-CoV-2 replication can be targeted by antivirals (Remdesivir), macrolide antibiotics such as azithromycin, and the anti-malarial hydroxychloroquine. Furthermore, hydroxychloroquine can help stabilize iron in hemoglobin (13).

Peptides are involved in most tissues for cell-to-cell communication. Several peptides, such as vasoactive peptides, have significant direct effects on vascular smooth muscle, blood flow, and thus blood pressure. These endogenous agents help the body's homeostatic mechanisms by regulating vascular compliance and vascular resistance. Vasoactive peptides, in addition to influencing vascular smooth muscle, act as neurotransmitters in the central nervous system (CNS) and systemic and local hormones. These compounds have G protein-coupled receptors (GPCR) and exert their physiological effects through these cell surface receptors (14).

The association of various vasoactive agents, such as Ang II, VIP, ET-1, CGRP, natriuretic peptides such as atrial natriuretic peptide (ANP), and brain natriuretic peptide (BNP), SP, and BK with COVID-19 pathophysiology will be probed in this article.

Vasoactive Peptides in COVID-19

Angiotensin II

Angiotensin II (Ang II) is a potent octapeptide, which acts as the main effector of the renin-angiotensin system (RAS). It plays a crucial role in homeostasis, control of blood pressure, and cardiac and vascular function (15).

In the classic RAS, the protease renin converts the substrate angiotensinogen to the decapeptide Ang I, and then,ACE removes two additional amino acids at the carboxyl terminus of Ang I to form Ang II (Figure 1) (10).

Nowadays two types of Ang II receptors have been recognized: AT1 and AT2. The AT1 receptor is the mediator of most of the established cardiovascular functions of Ang II such as vasoconstriction, increasing cardiac contractility, the secretion of aldosterone, and antidiuretic hormone with subsequent renal tubular sodium reabsorption, as well as inflammation, fibrosis, oxidative stress, and vascular and cardiac hypertrophy. But there is less data about the function of AT2. Nevertheless, there is some evidence which shows that stimulation of AT2 receptors exerts opposing and counterbalancing effects compared with AT1 receptors on the cardiovascular system, including, vasodilating effect, antihypertrophic effect, antifibrotic effect, and natriuretic effect (16).

So far, manipulation of the renin-angiotensin cascade has been considered as one of the major therapeutic strategies for patients with cardiovascular diseases and various clinical studies have evaluated the effect of angiotensin receptor blockers (ARBs) and ACE inhibitors (ACEIs) in different cardiovascular events such as refractory hypertension, heart failure, post-myocardial infarction status, and coronary artery disease. They are also used for patients with diabetes and renal insufficiency (17).

Another essential, regulatory enzyme in the renin-angiotensin pathway is ACE2 which is an ACE homolog. ACE2 has a zinc-binding site, which is homologous to one of the active domains of ACE. Generally, ACE2 and ACE have 40% similar identity, however, captopril or other 'classic' ACE inhibitors cannot inhibit the ACE2 enzyme. It is reported that ACE2 hydrolyze the his-leu bond of Ang I to produce Ang-(1-9). Then, Ang-(1-9) will be hydrolyzed by ACE but ACE2 does not hydrolyze Ang-(1-9) to Ang II. The other action of ACE2 is that it hydrolyzes Ang II to Ang-(1-7) at a high pace. Indeed, ACE2 decreases the accumulation of ANG II when it is needed but it does not do this action on Ang I (Figure 1) (10). The expression of the ACE2 receptor was found in many organs including the oral cavity, gastrointestinal tract, and lungs. The point is that the ACE2 membrane receptor functions as a binding site and the port of entry for SARS-CoV-2 virions on the lung cells. It was postulated that following the virus binding, ACE2 downregulation occurs, which in turn leads to a local raise in Ang II, and therefore, promoting RAS induction (18). The elevated level of the vasoconstrictor Ang II increases the production of thrombin and

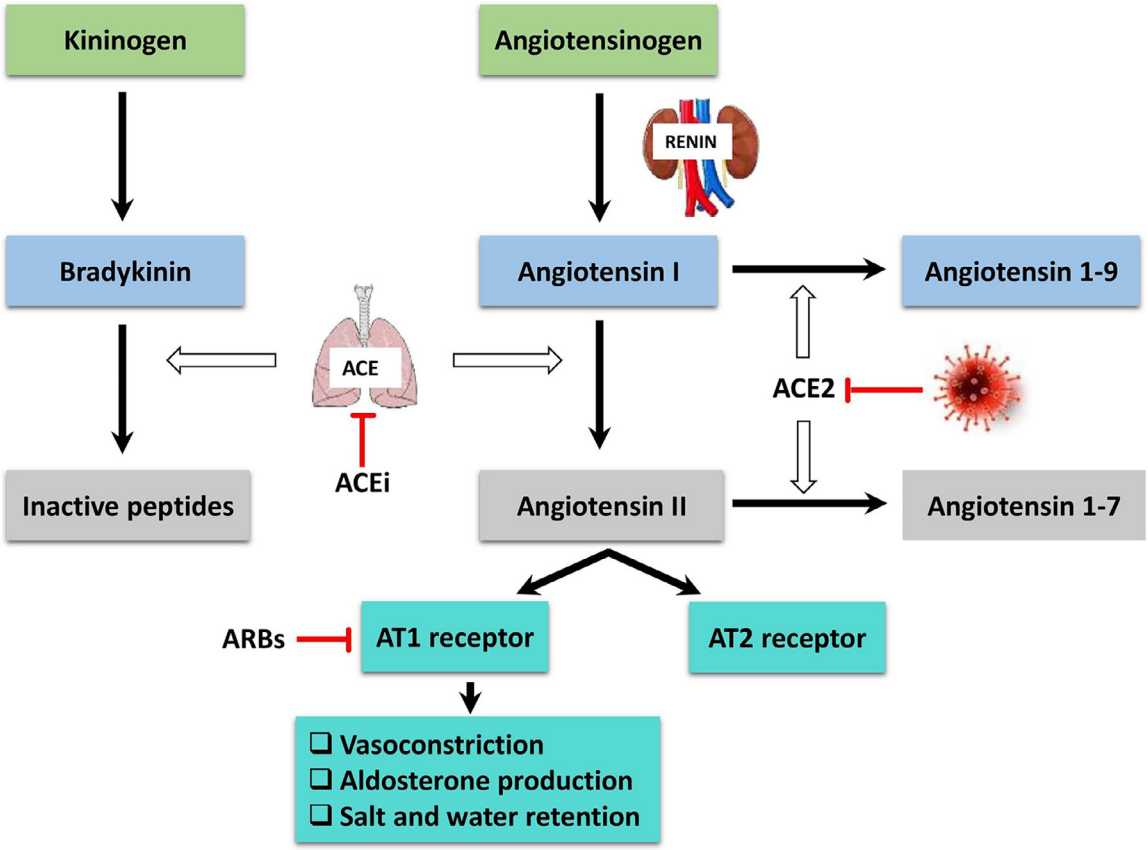

Figure 1. The renin-angiotensin system and action mechanisms of their inhibitor. ACE, angiotensin-converting enzyme; ACEi, ACE inhibitor; ARBs, angiotensin receptor blockers.

contributes to the impairment of fibrinolysis. Currently, it is strongly believed that in severe COVID-19, the increased Ang II is directly correlated with viral load and lung injury (19).

Animal experiments have shown that intravenous infusions of ACEIs and ARBs will raise the number of ACE2 receptors in the cardiopulmonary system (20). Then it is not surprising if patients who are consumers of ARBs and ACEIs become at an increased risk of diseases like SARS-COV-2 infection, as they have more binding sites for anchoring spike proteins on the exterior surfaces of coronavirus. However, there is no compelling clinical evidence to support such a notion about ACEIs or ARBs. Moreover, there are no data to support the notion that ACEI or ARB administration facilitates vulnerability to SARS-COV-2 infection or aggravates the severity of the disease, whereas it is recommended that hypertensive patients using ACEIs and/or ARBs should continue these medications during the coronavirus disease 2019 pandemic (21). Besides, in a recent study, it has been indicated that using ACEIs and ARBs through attenuating Ang II can induce the levels of Ang 1–7 as well as improve inflammation, fibrosis, and lung injury (22). To provide greater insights into the contribution of ACEIs and ARBs to this pandemic, future basic, clinical, and epidemiological investigations should further examine the links between the SARS-COV-2 and the RAS and how this might be affected by RAS inhibitors.

Vasoactive Intestinal Peptide

Vasoactive intestinal peptide (VIP), is a 28 amino acid peptide, which has a broad spectrum of physiological actions, including potent bronchodilatory and vasodilatory actions, enhancing blood circulation to the heart and lung, potent anti-inflammatory actions, modulation of airway epithelial secretions, inhibitory effects on vascular smooth muscle cell proliferation, cell growth and survival regulation (23). This large range of VIP effects is mainly mediated through two forms of 7 transmembrane G protein-coupled receptors: vasoactive intestinal receptor 1 and 2, which are also known as VPAC1 and VPAC2. The expression of these receptors can be widely found in the heart, blood vessels, lung, kidney, gastrointestinal tract, CNS, and other tissues (23).

There are some analogs of VIP which have long half-lives and are accessible for research use. For in-

stant stearyl-Nle-VIP is 100 times more potent than the original peptide. These drugs have been shown as novel therapeutic options for a vast variety of diseases such as gastrointestinal, pulmonary, cardiovascular, and nervous system diseases including Alzheimer's and Parkinson's disease (24,25).

The other example of VIP analogs is Aviptadil, which is a fully synthetic form of the 28 amino-acid VIP. It has been shown that using Aviptadil in pulmonary hypertension can cause modest and short-lived pulmonary vasodilation without affecting systemic blood pressure. Furthermore, VIP can be effective in other pulmonary disorders, for instance, it can be a modulator of lung inflammations (26) or many types of lung injury such as COPD (27). Reports show that VIP also has beneficial effects in sepsis-related acute respiratory distress syndrome (ARDS) and Sarcoid cases (28).

In an important recent investigation, it was found that patients with critical COVID-19 have elevated VIP plasma levels, compared with healthy subjects or asymptomatic patients, and the higher levels are correlated with further survival rate in those patients (29). Besides, the unique ability of VIP in the modulation of inflammation and apoptosis in Alveolar Type II cells (the target cells of the SARS-CoV-2) has been identified in numerous scientific studies (30). Based on another recent study, VIP is able to inhibit the SARS-CoV-2 virus gene replication in human lung epithelial cells, induce cytoprotective effects, promote monocyte production, and increase transmission of viral resistance from monocytes to neighboring lung cells (31). Currently, two available commercial dosage forms of synthetic VIP (Aviptadil in intravenous and inhaled formulation) are under two clinical trials for COVID-19 patients with respiratory failure (clinicaltrials.gov: NCT04311697 and NCT04360096).

Considering all the above-mentioned advantages, besides the exceptional safety profile of VIP and the affordable manufacturing of its synthetic forms, VIP could have the potential as a preventive measure and even therapeutic agent for patients with COVID-19 infection.

Endothelin

The endothelin (ET) isoforms comprise four structurally different 21 amino acid peptides including ET-1, ET-2, ET-3, ET-4). Mature ET-1 is considered as an endothelium-derived constricting factor, which is produced from pre-pro-ET-1 following the activities of a family of endothelin converting enzymes and other enzymes such as chymases, and endopeptidases (32). The current thinking is that the major source of ET-1 is vascular endothelial cells of various types of vessels, ranging from conduit and resistance arteries to large veins, and venules. Nevertheless, other cell types, such as epithelial cells in the lungs, colon, kidney, and colon; peripheral immune cells, as well as neurons and glial cells in the CNS produce ET-1 to some extent (33). ET-1 elicits its function through two isoforms of G-protein coupled receptors, ET_A and ET_B, with equal affinity. To date, it is generally accepted that ET-1 is among the most potent vasopressors known in the entire human cardiovascular system, and capable to produce great forceful pressor effects on a wide range of vessels (32,34).

Elevated circulating ET-1 levels have been detected in older ages, the male sex, and select ethnicities as well as in various pathological conditions such as hypertension, atherosclerosis, cerebrovascular diseases, and diabetes (35). Overall, it has been identified that older age, the male gender, and race/ethnicity could be considered important risk factors associated with COVID-19 mortality (36). On the other hand, since the COVID-19 pandemic started, a wealth of studies has indicated that the infected patients with pre-existing endothelial dysfunction, such as respiratory system diseases, hypertension, coronary heart disease, and diabetes, develop a higher rate of adverse outcomes (37). Besides, many reports have demonstrated the increased rate of vascular and thrombotic events (e.g., deep vein thrombosis, pulmonary embolism, and ischaemic stroke) in severe cases of COVID-19 (38,39). Therefore, regarding these associations between ET-1 with demographic features and a range of endothelial dysfunctions, it seems that increased circulating ET-1 levels might serve as a valuable biomarker and prognostic tool to identify individuals with the greatest risks for developing a serious illness from COVID-19 (37).

The crosstalk between the ET system and RAS has been shown through various investigations. It has been observed that the vasoconstrictive activity of Ang II could be suppressed by ET-receptor antagonists (40). On the other hand, as previously pointed out, the dysregulation of ACE2 plays a crucial role in the increased level of Ang II, which is strongly correlated with lung injury in SARS-CoV-2 patients. Nevertheless, Ang II activates the key transcriptional factor of ET-1, activator protein-1 (AP-1), resulting in the overexpression of ET-1, which may have a pivotal role in lung injury (41).

The redox-sensitive transcriptional factor, NF-kB is considered as another modulator of the ET-1 expression. Because of the severe inflammatory condition among COVID-19 cases, the role of NF-kB is highly regarded, and the efficacy of dexamethasone, the potent suppressor of NF-kB activity in the management of COVID-19 patients has been largely demonstrated. Besides, the effect of dexamethasone on the downregulation of ET receptors and ET-1 gene expression has been supported by a wealth of studies (42). Taken together, it seems that ET-1 has the potential to be considered as an important pathological factor, which can be therapeutically targeted in COVID-19.

Calcitonin Gene-related Peptide

Calcitonin gene-related peptide (CGRP) was initially identified in a paper by Amara SG, et al. in 1982 (43). It was soon realized that CGRP acts as a potent vasodilator, angiogenic, and immune-modulating peptide, which is primarily localized to the peripheral and central sensory nervous system (44). Because of its hypothesized function as a mediator of trigeminovascular pain transmission and vasodilator part of neurogenic inflammation, CGRP is a therapeutic goal in migraine. In 2018, CGRP antagonists, fremanezumab, and galcanezumab, were approved by the US Food and Drug Administration (FDA) for the prevention of migraines (45).

It has been shown that CGRP is correlated with perivascular neurons densely dispersed in myocardial and coronary arteries, which can lead to cardioprotective effects in conditions such as cardiovascular failure. It is widely believed that CGRP has crucial roles in anti-inflammatory and anti-apoptotic actions, as well as tissue repair, and the synthesis of the peptide is induced following an inflammatory response against tissue damage (44,46). Additionally, CGRP has been shown to exert potent pro-angiogenic, vasodilator, bronchoprotection, anti-inflammatory actions on lung tissue. These have made CGRP a promising target for manipulation in covid-19 patients (47).

Just recently, in a study by Ochoa-Callejero L, et al., it has been reported that the serum level of CGRP is remarkably reduced in COVID-19 positive individuals, comparing to healthy subjects, independently of the severity state of the disease, age, sex, or comorbidities (47). The lower levels of the vasoactive peptide may involve in vasoconstriction, the damaged epithelial repair, and impaired angiogenesis observed in lung pathology associated with COVID-19. They also found that the expression of the receptor activity modifying protein 1 (RAMP1), a subunit of CGRP receptor, is largely higher in COVID-19 lung samples, which may indicate a compensatory mechanism against the reduction of circulating levels of CGRP.

Surprisingly, there have been those who believe that over-release of CGRP may lead to the reported excessive reactivity of the vascular system in acute lung injury. In a research investigating the impact of CGRP on acid-induced lung injury, it has been indicated that CGRP gene-disrupted mouse has substantially attenuated acid-induced trauma, edema, and respiratory failure relative to healthy controls (48). Moreover, in studies on ovine models of burn and smoke inhalation, it has been indicated that CGRP inhibition by disrupting the endogenous CGRP pathway may have a therapeutic role in respiratory malfunction (49).

The SARS-CoV2 is currently suspected of triggering a form of cytokine tempest, including fever, thrombocytopenia, lymphopenia, coagulopathy, macrophage activation, ARDS, and multi-organ inadequate septic shock (50). Early studies indicate that the rise in interleukin-6 (IL-6) may lead to augment the invasiveness of COVID-19 and some proposed that it could be used as a marker for the intensity evaluation (51). Also, the IL-6 blockade has been proved to be effective as a therapy for hyperinflammatory reactions in patients with COVID-19 and further studies are underway (52). CGRP also knows to have stimulatory effects on the production of proinflammatory cytokines, such as IL-6 (53). Collectively, these may strengthen the rationale of repurposing the CGRP receptor antagonist to treat COVID-19 patients. However, concerning the cardiopulmonary protective effects of CGRP, as mentioned before, there are still some doubts related to the safety of CGRP inhibitors in COVID-19. Much more studies are needed to optimize the therapeutic approach targeting the CGRP pathway against COVID-19 infection.

Natriuretic Peptides

Natriuretic peptides are a group of circulating peptide hormones, which serve as key regulators of cardio-renal homeostasis and multiple metabolic processes (54). Until now, there have been eight natriuretic peptides including ANP, BNP, C-type natriuretic peptide (CNP), Dendroaspis natriuretic peptide (DNP), urodilatin, uroguanylin, osteocrin, and musculin. These peptides are primarily released by the heart and are well known as cardiac hormones. Natriuretic peptide receptor (NRP) family containing NPR-A (guanylate cyclase-A), NPR-B (guanylate cyclase-B), and NPR-C (clearance receptor) is the mediator of the main biological actions of the peptides (for instance vasodilation, natriuresis, and metabolic regulation) in their target tissues (54). Consistently, their plasma levels are frequently used as diagnostic and prognostic biomarkers in patients with cardiovascular disease such as heart failure and pulmonary embolism. Besides, the therapeutic potential of the synthetic derivatives of natriuretic peptides has been shown in several cardiovascular disorders, particularly in heart failure (55). On the other hand, the lung-protective effects of these peptides have been suggested through accumulating experimental and clinical studies. For example, so far, numerous studies have implicated the beneficial effects of ANP on inhibiting the increased endothelial permeability and secretion of inflammatory mediators induced by several insults, such as thrombin, LPS, TNFα, and oxidative stress (56). Further, the therapeutic role of ANP in a clinical study conducted by Mitaka C, et al. has been demonstrated in ARDS in patients with acute lung injury (57). Emerging evidence indicates that pulmonary vascular endothelial injury plays a pivotal role in the COVID-19 pathogenesis (58).

In addition to cardiovascular disorders, the presence of deficiencies of the natriuretic peptide levels is also evident in obese and elderly subjects. As previously pointed out, comorbidities of cardiovascular disease, old age, and metabolic disorders are associated with poor clinical out-

comes and higher mortality in COVID-19-infected patients. It is postulated that dysregulation of the natriuretic peptide system may also contribute to COVID-19 patients.

Taken together, pharmacological strategies augmenting natriuretic peptide signaling may be effective in preventing the progression of the infection to severe respiratory disease and the need for ventilator therapy. Moreover, reinforcement of the natriuretic peptide system in COVID-19 patients could result in several other beneficial outcomes, including cardioprotection, preventing coagulopathy, natriuresis, and subsequent attenuating lung edema and the risk of renal injury. In support of this notion, nine ongoing clinical trials are exploring the effect of inhaled nitric oxide, as a stimulus of cGMP production through soluble guanyl cyclase, on COVID-19-infected patients (clinical trials.gov: NCT04383002, NCT04338828, NCT04358588, NCT04305457, NCT04305457, NCT04337918, NCT04306393, NCT04421508, NCT04398290) (56).

Currently, there are two therapeutic approaches targeting the natriuretic peptide pathway in patients with COVID-19. Firstly, using Sacubitril, as an oral endopeptidase inhibitor, which is able to increase the circulatory levels of neprilysin-degraded peptides, such as ANP and BNP (59). The second choice is the synthetic derives of the peptides, including Carperitide (ANP) and Nesiritide (BNP) for intravenous infusion (60).

Under physiological conditions, BNP, and the N-terminal fragment of its precursor (NT-proBNP), are secreted by stressed cardiomyocytes in the heart ventricles following increased ventricular blood volume. Accordingly, their raised levels are considered as important indicators of the failing heart (61).

Likewise, COVID-19 is often demonstrated with higher levels of BNP or NT-proBNP. Therefore, the diagnostic value of the peptide in predicting the prognosis in patients infected with COVID-19 has been suggested in several studies (62). Recently, Sorrentino S, et al. in a meta-analysis of 13 observational studies and a total of 2248 patients indicated that there is a robust positive relationship between the increased NT-proBNP level assessed on the admission of COVID-19 patients and the severity of the disease (63). Besides, in a large retrospective study conducted on Chinese COVID-19 patients, it was suggested that a combination of the two cardiac injury biomarkers, high-sensitivity cardiac troponin I and NT-proBNP, would be more valuable than the individual biomarkers alone in determining the prognosis of COVID-19 patients and the in-hospital mortality (64).

Substance P

Substance P (SP) is a neuropeptide consisting of 11 amino acid residues and belongs to the tachykinin neuropeptide family (65). The biological effects of SP are mediated by its receptor, neurokinin type 1 receptor (NK-1R) which consisting of seven transmembrane domain GPCR. NK-1R is expressed in the CNS and peripheral nervous systems (PNS) as well as endothelial cells, epithelial, lymphatics, leukocytes, smooth muscle cells, and fibroblasts (66). Although in the nervous system, SP acts as a neurotransmitter/neuromodulator in pain perception, regarding the wide distribution of SP and its receptor, SP through interaction with NK1R is participated in regulating different mechanisms such as inflammatory and immune response, hematopoiesis, vasodilation, chemotaxis, cell survival, and proliferation as well as play roles in the respiratory, gastrointestinal, urogenital, cardiovascular systems and tumors (65,67).

Furthermore, SP is involved in the pathological process of respiratory diseases such as asthma and chronic obstructive pulmonary diseases (COPD). Activation of NK-1R induces constriction of airway smooth muscle, leading to reduction of airway diameter and degranulation of mast cell in lung tissue (68). Likewise, it has been indicated SP is contributed to multiple viral infection pathogenesis through pro-viral actions (69). SP is elevated in lymphocytes in the lung in response to viral infection and anti-SP antibodies reduced inflammatory responses to pulmonary viral infection including decreased infiltration of inflammatory cells as well as decrease pro-inflammatory cytokines expression level (70,71). On the other hand, it has been indicated that viruses could lead to induction of SP and neurogenic inflammation, especially in the lungs with the respiratory challenge (72,73). Since SP induces the degranulation of mast cells and neutrophils, it appears application of NK-1R antagonists may inhibit recruitment of immune cells such as neutrophils and respiratory burst activity, and finally attenuate inflammation in COVID-19 patients (74).

SP highly expressed in the nucleus tractus solitarius and the area postrema and both activation stimulate the vomiting reflex (67). NK-1R antagonists, aprepitant and fosaprepitant, block SP binding to its receptor and consequently inhibit vomiting centrally in the chemoreceptor trigger zone which is used for managing chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV) (75). Therefore, it seems inhibition of activation of NK-1R maybe is effective for COVID-19-induced nausea and vomiting.

SP promotes viral pathogenesis through increase inflammatory processes in involved sites in inflammation in infected patients with SARS-CoV-2 including the respiratory system, digestive system, and skin (74). SP and the complement peptides C3a and C5a in a similar manner stimulate mast cells by different pathways. Furthermore, there is a synergism between C5a and SP to activation and recruitment of neutrophils to the infection site (74). SP independent of the NK-1R can bind to mast cell receptor called Mrgprb2, leads to facilitation recruitment and migration of immune cells via Mrgprb2. Furthermore, activation of mast cell by SP cause to the release of mul-

tiple pro-inflammatory cytokines and chemokines. Therefore, SP-mediated inflammatory responses can be independent of NK-1R (76). Moreover, COVID-19 patients exhibit coagulation abnormalities and blood clots in the small vessels of the various tissues which are causes of strokes and heart attacks. SP increases monocyte tissue factor expression, the main initiator of the coagulation cascade, and promotes platelet clot formation (77,78). Overall, these activated pathways may play an important role in the recruitment of neutrophils and inflammatory responses in covid-19 patients. In accordance with the above-mentioned, SP can participate in COVID-19 symptomology. Therefore, inhibition of substance P can be a target in COVID-19 patients and it seems the use of inhibitors to SP, NK-1R, or the downstream pathways may offer supportive treatment and attenuate inflammatory response in COVID-19 patients (74).

The enzyme neutral endopeptidase or neprilysin (NEP) is a member of zink-metalloendopeptidase which is widely expressed in the kidney, lung, and other tissues such as the breast, prostate, stomach, and CNS. Regarding NEP exert protective roles against pulmonary inflammation and fibrosis, it is proposed NEP activity augmentation potentially have may attenuate COVID-19 pathology (79,80). In this context, it has been shown that NEP possesses catalytic activity rather than ACE2 in cleavage of the vasoconstrictor peptides Ang I and AngII into vasodilator peptide Ang 1–7 (81). NEP is also involved in the inhibition of recruitment of more neutrophils into the site of injury via its catabolic action on the gastrin-releasing peptide (GRP) during pulmonary inflammation (79). However, on the other hand, NEP is a key enzyme in the degradation of natriuretic peptides, bradykinin (BK), SP, and adrenomedullin (ADM), and apelin that account for the prevention of organ injury (80).

Bradykinin

The kallikrein-kinin system (KKS) is involved in blood pressure regulation, inflammatory responses, pain, coagulation, and cell proliferation. The kinin peptides through release vasodilators including prostaglandin E2, and PGI2, nitric oxide (NO), and endothelial-derived hyperpolarizing factor (EDHF) induce increase vascular permeability and arteriolar dilation in the vascular bed such as skeletal muscle, liver, kidney, heart, intestine. Furthermore, kinins cause veins contraction by vasoconstrictors such as PGF2α. The kinin peptides effect is mediated through specific two distinct G-protein coupled receptors termed bradykinin receptors B1 and B2 (82).

The KKS comprises serine proteases called plasma kallikrein and tissue kallikrein, which cleavage specific substrates kininogens to produce kinins, principally bradykinin (BK) and Lys-bradykinin (Lys-BK or kallidin) (83). The nonapeptide BK is formed via activation of plasma kallikrein on high molecular weight kininogen (HMWK), while tissue kallikrein cleaves low-molecular-weight kininogen (LMWK) to decapeptide Lys-BK (84). BK and Lys-BK bind with the B2 receptor on the endothelial cells. BK and Lys-BK by kininase I or kininase II (also known as AEC) can be cleaved again to produce kinins metabolites, des- Arg BK (DABK) and Lys-des-Arg BK (Lys-DABK) which are ligands of the B1 receptor on the endothelial cells (84,85). The B2 receptor is constitutively expressed by most cells including vascular and non-vascular smooth muscle cells, epithelial and immune cells, and neural cells. On contrary, the B1 receptor poorly is expressed in physiological conditions and their expression is elevated in inflammatory conditions (84). Both receptors can couple to Gαi and Gαq families lead to increased intracellular Ca2+ and consequently release nitric oxide (NO), arachidonic acid, prostaglandins, and leukotrienes (86). The principal ligand of B1 is DABK and the principal ligand of B2 is BK. Degradation of kinins is controlled through ACE1 that cleaves BK and ACE2 that cleaves Lys-des-Arg9-BK and des-Arg9-BK (87).

B1 stimulation, as an inducible receptor, is involved in the pro-inflammatory responses and leads to vasoconstriction which contributes to organ injury including acute respiratory distress syndrome (ARDS). On the other hand, B2 activation by BK on endothelial cells may lead to capillary permeability and leakage, and in resulting angioedema (88). Furthermore, The B2 or B1 stimulation differentially activates endothelial NO synthase (eNOS) or inducible NO synthase (iNOS), respectively. Under inflammatory conditions, B1 stimulation leads to prolonged activation of iNOS and high output NO production with deleterious organ effect, while in normal endothelial cells, the B2 activation results in eNOS activation and a short burst of NO with protective organ effects (85). The B1 receptor expression is very sensitive to inflammatory factors such as interleukins and lipopolysaccharide and it could be up-regulated via cytokines like IL-1β and TNFα. it has shown that B1 activation via the release of chemokine CXCL5 increases recruitment of neutrophils as well as causes FGF-2 expression, and upregulated IL-1β and MCP-1 levels (89). DABK is one of the pulmonary inflammatory mediators. ACE2 can deactivate DABK by cleaves the terminal residue of DABK. Therefore, since ACE2 cleaves DABK, reduction in activity or expression of ACE2 by virus leads to impairment of the inactivation of DABK.

According to the above mentioned, it appears that SARS-CoV-2 through the decrease of ACE2 activity leads to an increase of free DABK, enhanced its signaling on B1 receptor, and subsequent stimulation of B1 receptor can cause fluid extravasation, recruitment of leukocyte and neutrophils to the lung, potentiation of the inflammatory cascade, and as well as the release of pro-inflammatory mediators (Figure 2) (87,90). It has proposed that may be dysregulation of KKS participates in COVID19 patho-

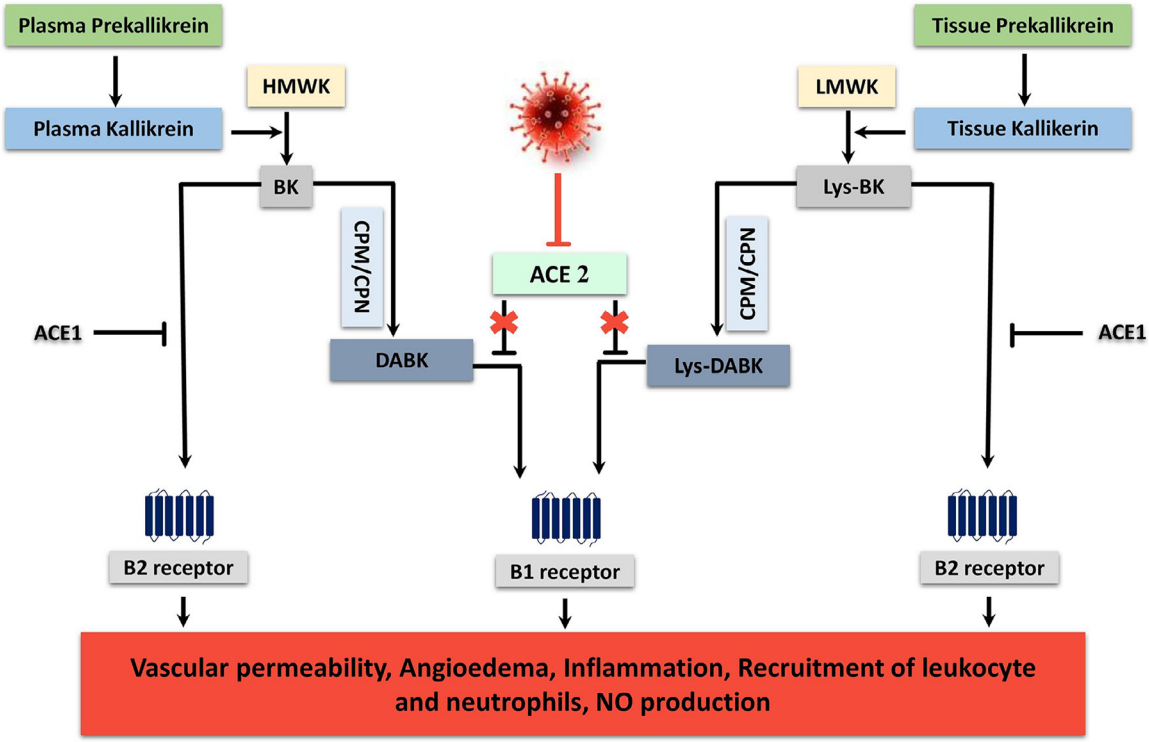

Figure 2. The kallikrein-kinin system (KKS) and proposed effects of SARS-CoV-2 on related pathways. BK, bradykinin; Lys-BK, Lys-bradykinin; DABK, des-Arg BK; Lys-DABK, Lys-des-Arg BK; HMWK, high molecular weight kininogen; LMWK, low-molecular-weight kininogen; CPM, carboxypeptidase M; CPN, carboxypeptidase N; ACE, angiotensin-converting enzyme.

genesis via the downregulation of ACE2 function in the lung and therefore targeting the kallikrein-kinin pathway in patients with COVID-19 through block B1 and B2 receptors is an effective strategy signaling to prevent ARDS (88). Since downregulation of ACE2 expression induced SARS-CoV infection enhances the half-life of DAB or DABK which leading to pulmonary edema in COVID-19 patients, it seems inhibition of B2 signaling by icatibant and lanadelumab exert promising result in infected patients (91). Furthermore, inhibition of B1 by LF22-0542 (safotibant), as a B1 antagonist, maybe alleviate a part of the cytokine storm in COVID-19 infected patients (87).

Excess BK can alter electrolytes amount such as potassium and cause hypokalemia, which in turn is associated with arrhythmia and sudden cardiac death. According to recent report patients with severe COVID-19 display hypokalemia and resulting in its complications is occurring in infected patients (92). Additionally, many COVID-19 symptoms including fatigue, headaches, nausea, myalgia, diarrhea, vomiting, and anorexia are very similar to a high level of BK which is associated with increases vascular permeability such as angioedema (88). Therefore, SARS-CoV-2 pathology may be the result of BK storms rather than cytokine storms. However, the BK storm and cytokine storms hypotheses are linked because IL-2 has been shown to be upregulated via BK (88,93). The KKS disruption also is detected in chronic kidney disease, cardiovascular disease, and Alzheimer's disease that these conditions might enhance the risk of COVID-19 (74).

Snake venoms are very poisonous mixtures of a variety of molecules, such as carbohydrates, nucleosides, amino acids, peptides, proteins, and lipids. Although snake venoms may be lethal, they are rich biological resources with antiviral activities. antiviral properties of snake venoms components have been shown against viruses of measles, Sendai, dengue, yellow fever virus (YFV), and HIV (94). BK-potentiating peptides (BPPs) extracted from snake venoms such as Bothrops venom are natural BK agonists and ACE inhibitors and show remarkable organ protective effects by targeting RAS and KKS systems. Surprisingly, BPP-10 c is reported safe and without cytotoxic effects and can through ACE inhibition leads to increase BK effects via the B2 receptor, promotes NO-mediated organ protective effects, reduces inflammatory response, protects neurons, and also acts as an antihypertensive. (85,95). Therefore, regarding antiviral effects of BPP-10 c, it is exhibited

a great value as a natural option to attenuate SARS-CoV-2 related consequences (85).

Conclusion

The COVID-19 pandemic is an emerging rapidly evolving outbreak, and there is an unprecedented timeline for developing effective drugs to manage the disease. Currently, a wide range of experimental and clinical studies investigating the therapeutic and biomarker potential of the vasoactive peptides in the management of COVID-19 complications, particularly ARDS and cardiovascular comorbidities, which remains to be proven, is ongoing. Changes in most of these peptides are linked to the presence of the disease and a more severe prognosis. Therefore, using vasoactive peptides as indicators or therapeutic targets may be beneficial to understand the COVID-19 pathogenesis and to modulate the post-infection immune response to limit coronavirus-associated complications and mortality.

Conflict of Interest

Authors have no conflict of interest.

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