

REVIEW

Snake venom-derived bradykinin-potentiating peptides: A promising therapy for COVID-19?

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Abstract

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a novel coronavirus responsible for the recent infectious pandemic, is known to downregulate angiotensin-converting enzyme-2 (ACE2). Most current investigations focused on SARS-CoV-2-related effects on the renin-angiotensin system and especially the resultant increase in angiotensin II, neglecting its effects on the kinin-kallikrein system. SARS-CoV-2-induced ACE2 inhibition leads to the augmentation of bradykinin 1-receptor effects, as ACE2 inactivates des-Arg⁹-bradykinin, a bradykinin metabolite. SARS-CoV-2 also decreases bradykinin 2-receptor effects as it affects bradykinin synthesis by inhibiting cathepsin L, a kininogenase present at the site of infection and involved in bradykinin production. The physiologies of both the renin-angiotensin and kinin-kallikrein system are functionally related suggesting that any intervention aiming to treat SARS-CoV-2-infected patients by triggering one system but ignoring the other may not be adequately effective. Interestingly, the snake-derived bradykinin-potentiating peptide (BPP-10c) acts on both systems. BPP-10c strongly decreases angiotensin II by inhibiting ACE, increasing bradykinin-related effects on the bradykinin 2-receptor and increasing nitric oxide-mediated effects. Based on a narrative review of the literature, we suggest that BPP-10c could be an optimally effective option to consider when aiming at developing an anti-SARS-CoV-2 drug.

KEYWORDS

COVID-19, kinin-kallikrein system, snake-derived bradykinin-potentiating peptide

1 | INTRODUCTION

A novel frightening coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has spread worldwide since December 2019. COVID-19 is mainly a contagious acute respiratory infection that can lead to life-threatening presentations and fatalities (Phan et al., 2020). On March 2020, the World Health Organization declared that the outbreak is a pandemic (Habibzadeh & Lang, 2020). On mid-June 2020, the total number of reported cases worldwide was ~7.7 million causing ~430,000 deaths (Worldometers.Info).

To date, an unbelievable number of research projects have been conducted. Full-length genome analyses of SARS-CoV-2 were

obtained concluding its 96% identity with bat coronaviruses (Zhou et al., 2020). Studies of the virus relative synonymous codon usage bias revealed closeness to the snake, suggesting that snake may be an animal reservoir (Ji, Wang, Zhao, Zai, & Li, 2020). Researchers are currently investigating infectivity, mode of transmission, mechanisms of disease and clinical effects aiming at identifying effective therapeutic and preventative options. Clinical trials are in process to test various anti-SARS-CoV-2 therapies; but none is yet approved (Ahsan, Javed, Al Bratty, Alhazmi, & Najmi, 2020).

SARS-CoV-2, a positive-stranded RNA virus, contains major structural proteins including the spike (S), envelope (E), membrane (M) and nucleocapsid proteins (Wu et al., 2020). SARS-CoV-2 spike protein interacts with an epithelial cell surface receptor identified as

the angiotensin-converting enzyme-2 (ACE2) allowing the virus to enter cells and cause the infection (Walls et al., 2020). SARS-CoV-2/ACE2 interaction rapidly induces ACE2 downregulation (Hoffmann et al., 2020; Silhol, Sarlon, Deharo, & Vaïsse, 2020). ACE2 is a zinc-containing metalloenzyme expressed predominantly at the membrane surface of vascular endothelial cells, type II pneumocytes and various epithelial cells (Sodhi et al., 2018). ACE2 expression correlates with sites of infection including lung and intestine (Hamming et al., 2004), consistent with COVID-19-related main respiratory and intestinal manifestations (Xu, Zhou, & Xu, 2020).

Almost all studies interpreted the COVID-19-attributed ACE2 downregulation and the subsequent inflammation as related to the renin-angiotensin system (RAS) dysfunction (Gurwitz, 2020; Hoffmann et al., 2020; Lu et al., 2020). Rare studies suggested COVID-19-associated kinin-kallikrein system (KKS) dysregulation as potential trigger for the observed inflammation mediated by the innate immune response (van de Veerdonk et al., 2020). The role of ACE2 is crucial since its altered activity affects both RAS and KKS (Gralinski et al., 2018; Kuba et al., 2005; Sampaio et al., 2007; Santos et al., 2003; Sodhi et al., 2018; Yang, Yin, Li, Zimmerman, & Schultz, 2011). Here we aimed to review the involvement of both systems in COVID-19 pathogenesis and discuss the potential usefulness of the snake-derived bradykinin-potentiating peptides (BPPs), able to interact with both systems, as optimal anti-COVID-19 therapy.

2 | THE RAS

The RAS regulates blood pressure, systemic vascular resistance and electrolyte balance. Briefly, the renal juxtaglomerular cells secrete renin when the renal blood flow decreases. Plasma renin converts angiotensinogen released by the liver to angiotensin I that subsequently convert angiotensin I to angiotensin II by ACE present at the vascular endothelial cell surface (Figure 1). Angiotensin II is a potent vasoconstrictor and stimulates aldosterone production from the adrenal cortex.

ACE1 degrades angiotensin I to angiotensin II, which acts through the angiotensin I-receptor (AT1R; Kuba et al., 2005). Angiotensin II/AT1R stimulates the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway to exert its vasoconstriction and hypertensive activity (Recinos et al., 2007). Additionally, angiotensin II/AT1-R activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signaling pathway, increases the production of reactive oxygen species (ROS), induces immune cell infiltration and increases the production of C-reactive protein and proinflammatory cytokines such as the tumor necrosis factor-alpha (TNF- α), interleukins (IL)-1, -6, and interferon (IFN)- γ in target tissues (Han, Liu, Liu, & Li, 2010; Lee et al., 2014). Angiotensin II/AT1R-related stimulation of ROS generation results in nitric oxide (NO) breakdown leading to endothelial dysfunction (Griendling, Lassègue, Murphy, & Wayne Alexander, 1994). Angiotensin II activates mitogen-activated protein kinase (MAPK) signaling cascade leading to phospholipase A2 (PLA2) activation (Kaschina &

Unger, 2003). This activation enhances the secretion of arachidonic acid which mediates various signaling (generated by cytosolic PLA2) and inflammatory processes (generated by secretory PLA2; Baynes & Dominiczak, 2005). Arachidonic acid is metabolized to eicosanoids as prostaglandins, prostacyclin (by the action of cyclooxygenase 1 and 2), and leukotrienes and thromboxanes (by the action of prostaglandin G/H synthase-1 and 2), which regulate the immunopathological processes of inflammatory responses (Harizi, Corcuff, & Gualde, 2008). Angiotensin II/AT1R causes vasoconstriction, increased vascular permeability, inflammation and fibrosis (Kuba et al., 2005). Angiotensin II enhances arterial vascular thrombosis in arterioles by modulating plasminogen activation mediated by enhanced plasminogen activator inhibitor type 1 (PAI-1) expression (Senchenkova, Russell, Almeida-Paula, Harding, & Granger, 2010) and thromboxane production (Smith & Song, 2002).

ACE2 degrades angiotensin II to generate angiotensin (1-7) which subsequently acts through the mas oncogene product (MAS) receptor to counteract angiotensin II/AT1R effects and stimulate NOS (Sampaio et al., 2007). Angiotensin 1-7 stimulates AT2R which has vasodilatory, antiproliferative, antiinflammatory and antifibrotic effects (Calò, Rigato, & Bertoldi, 2019; Chappell & Al Zayadneh, 2017; Katovich, Grobe, & Raizada, 2008; Rodrigues Prestes, Rocha, Miranda, Teixeira, & Simoes-e-Silva, 2017). Angiotensin 1-7 can be inactivated by ACE to inactive angiotensin 1-5 (Santos, Ferreira, & Simões e Silva, 2008). Noteworthy, angiotensin (1-7) can be directly synthesized from angiotensin I by neprilysin (Chappell, 2016), thimet oligopeptidase (Wilson, Nautiyal, Gwathmey, Rose, & Chappell, 2016), prolylendopeptidase and metalloendopeptidase (Deddish et al., 1998).

ACE has two homologous N- and C-domains, present at the N-terminal half (N-ACE) or the C-terminal half (C-ACE) of the single-chain protein, respectively. Angiotensin (1-7) is both ACE substrate and inhibitor. It is degraded mainly by N-ACE and more slowly by C-ACE and inhibits C-ACE, which mainly hydrolyzes bradykinin and angiotensin I (Deddish et al., 1998).

Collectively, ACE metabolizes angiotensin I to angiotensin II (which induces vasoconstriction, ROS production, immune cell infiltration, inflammatory response, vascular permeability, thrombosis and fibrosis), while ACE2 metabolizes angiotensin II to angiotensin (1-7) (which counteracts angiotensin II and presents vasodilatory, antiproliferative, antiinflammatory and antifibrotic effects).

3 | THE KKS

KKS is a poorly understood hormonal system consisting of blood proteins including bradykinin and kallidin and implicated in inflammation, blood pressure control, coagulation and pain (Figure 1). Kininogens are processed by two types of serine-proteases called kallikreins and released as part of innate inflammation. Plasma kallikrein processes high-molecular-weight kininogen (HMWK) to bradykinin and tissue kallikrein processes kinins from low-molecular-weight kininogen (LMWK) to Lys-bradykinin. Both bradykinin and Lys-bradykinin interact with the bradykinin receptor-B2 (B2R) on the endothelial cells.

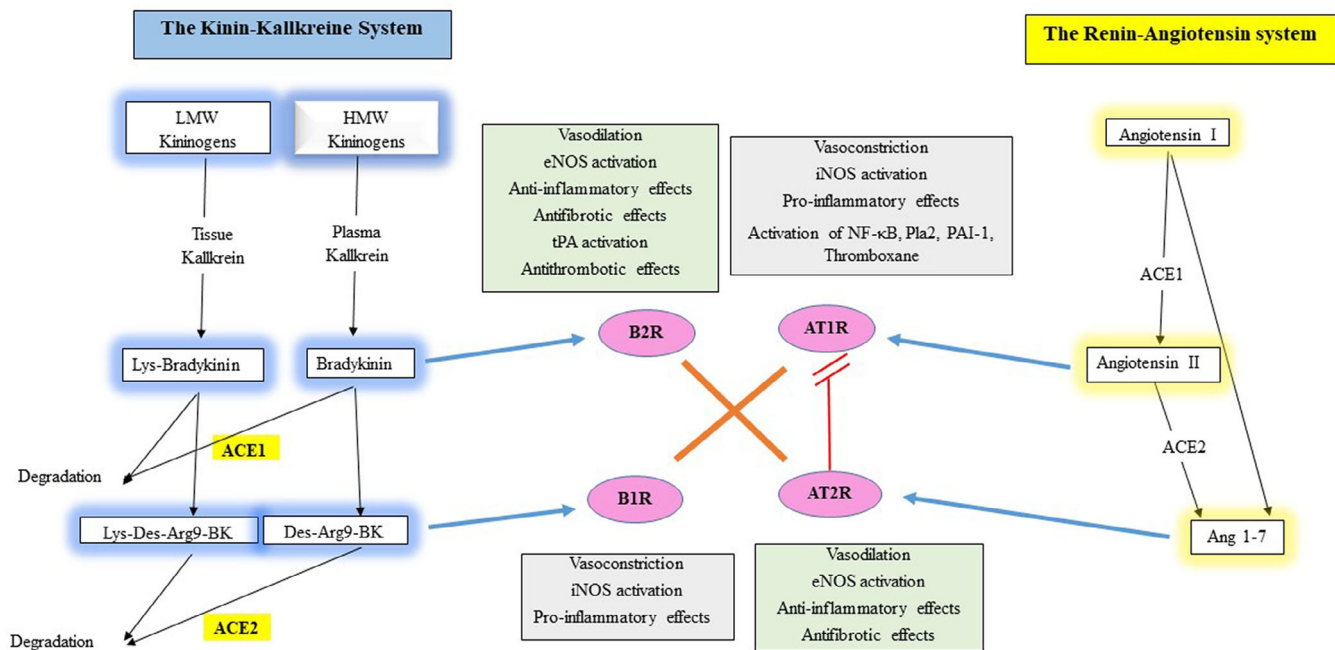


FIGURE 1 The physiology and functional relationships between the renin angiotensin and KKSs

They can both be further processed to des-Arg9-bradykinin (from bradykinin degradation by carboxypeptidase M [CPM]) and Lys-des-Arg9-bradykinin (from Lys-bradykinin degradation by carboxypeptidase N [CPN]), which are ligands of the bradykinin receptor-B1 (B1R), also present on the endothelial cells and upregulated under inflammatory conditions (Jurado-Palomo & Caballero, 2017).

B2R agonists are considered as potent vasodilators and organoprotective peptides (Heitsch, 2002). B2R inhibits adenylate cyclase, stimulates phospholipase C that subsequently increases intracellular free calcium and provokes endothelium-dependent vasodilation by inducing local NO production (Fernandes et al., 2001). B2R stimulation also results in prostacyclin production and increase in endothelium-derived hyperpolarizing factor and tissue plasminogen activator (tPA; Ancion, Tridetti, Nguyen Trung, Oury, & Lancellotti, 2019). Endothelial NO production triggered by bradykinin plays an organoprotective role by limiting leukocyte adhesion/migration, platelet adhesion/aggregation and smooth muscle contraction/proliferation (Hällgren, Samuelsson, Laurent, & Modig, 1989). Deficient NO bioavailability resulting from reduced NO production by the endothelial NO synthase (eNOS) and increased NO breakdown by ROS are associated with endothelial dysfunction (Tomasian, 2000). Additionally, NO possesses an antiapoptotic activity (Baudin, Berard, Carrier, Legrand, & Drouet, 1997).

Bradykinin is considered to be a potent stimulator of tPA secretion, thus affecting fibrinolysis and thrombolysis (Brown, Nadeau, & Vaughan, 1997). t-PA/PAI-1 balance controls thrombi formation and degradation (Bentley et al., 2010). Increases in PAI-1 and decreases in t-PA are associated with thrombi formation (Wiman et al., 2000). Bradykinin has antithrombotic effects by increasing t-PA by an independent direct pathway based on NO production (Rahman et al., 2014).

B1R, poorly expressed on endothelial cells in physiological conditions, is upregulated in proinflammatory conditions (Heitsch, 2002). B1R and B2R have different functions (Wu, Lin, Bernloehr, Hildebrandt, & Doods, 2012). B1R stimulation induced by cytosolic calcium ion contributes to the inflammatory responses (Gurusamy et al., 2016). B1R stimulation has detrimental effects by enhancing the proinflammatory response and causing vasoconstriction that contributes to organ injury including acute respiratory distress syndrome (ARDS; Murugesan et al., 2016; Qadri & Bader, 2018). Moreover, B1R stimulation results in prolonged inducible NO synthase (iNOS) activation which is responsible for prolonged high NO output and deleterious organ effect, whereas B2R stimulation results in eNOS activation which is responsible for short burst of NO and protective organ effects (Erdös, Tan, & Skidgel, 2010; Kuhr, Lowry, Zhang, Brovkovich, & Skidgel, 2010). Kinin-B1R overexpression induces hypertensive response to Des-Arg9-bradykinin and susceptibility to inflammation (Ni et al., 2003).

Kinin degradation is controlled by ACE1 that inactivates bradykinin and ACE2 that inactivates Lys-des-Arg9-bradykinin and des-Arg9-bradykinin to decrease their effects on B2R and B1R, respectively (Sodhi et al., 2018). ACE1 inhibition, which results in increased bradykinin effects on B2R, has been associated with systemic angioedema (Jurado-Palomo & Caballero, 2017). ACE2 inhibition, which increases the effects of Lys des-Arg9-bradykinin and des-Arg9-bradykinin on B1R, leads to proinflammatory effects associated with pulmonary edema and acute lung injury (Imai et al., 2005; Sodhi et al., 2018).

Collectively, kallikreins processes kininogens to bradykinins. Bradykinins act through endothelial B2R (inducing vasodilation and organoprotective effects) and are further processed to des-

bradykinins which act on B1R which is upregulated in inflammatory conditions (inducing vasoconstriction and inflammatory response). ACE1 inactivates bradykinins and ACE2 inactivates des-bradykinins.

4 | FUNCTIONAL RELATION BETWEEN RAS AND KKS

Studies showed that angiotensin 1–7 and bradykinin actions are strongly interrelated. Angiotensin (1–7) potentiates bradykinin-induced vasodilation on B2R by inhibiting ACE and releasing NO (Fernandes et al., 2001; Greco, Master Jr, F, Baber, & Kadowitz, 2006; Li, Chappell, Ferrario, & Brosnihan, 1997). Other studies reported that bradykinin/NO cascade mediates AT2R stimulation (Gohlke, Pees, & Unger, 1998; Siragy & Carey, 1996). There is a heterodimerization and strong functional interaction between MAS and AT2R suggesting that they depend on each other (Leonhardt et al., 2017). Bradykinin/NO system mediates counteraction between AT1R and AT2R (Searles & Harrison, 1999). Experimental studies correlated B2R-attributed organoprotective role and AT1R-attributed counteracting effects (Taddei & Bortolotto, 2016). B2R is considered as a physiological antagonist of angiotensin II-related effects on AT1R (Alhenc-Gelas et al., 2011). This indicates that the functional activities of angiotensin 1–7 (on MAS receptor and AT1R) and bradykinin (on B2R) depend on each other. Also, angiotensin (1–7) can indirectly potentiate B2R by binding to the active site of ACE, thus blocking bradykinin degradation (Deddish et al., 1998). Finally, the action of AT1R and B1R are functionally interrelated. AT1R can synergize B1R-related effects by ROS induction in the endothelial cells (Ceravolo et al., 2014). The functions and relations between RAS and KKS are shown in Figure 1.

5 | IMPLICATIONS OF RAS AND KKS IN COVID-19

ACE2 inhibition affects both RAS and KKS as it decrease degradation of angiotensin II to angiotensin 1–7 and decreases degradation of Lys des-Arg9-bradykinin and des-Arg9-bradykinin, leading to increase in functionally interrelated angiotensin II (through effects on AT1R) as well as Lys des-Arg9-bradykinin and des-Arg9-bradykinin (through effects on B1R). ACE2 inhibition limits the functions of the functionally interrelated angiotensin 1–7 (through effects on MAS receptor and AT2R) and bradykinin (through effects on B2R). The effects of SARS-COV-2 on both RAS and KKS are shown in Figure 2.

It is important to consider the role of cathepsin L, a lysosomal cysteine endopeptidase that strongly enhances KKS involvement in COVID-19 pathogenesis. Cathepsin L mediates SARS-COV-2 cell entry through the transmembrane protease serine-2 (TMPRSS2; Hoffmann et al., 2020). Consistently, cathepsin L was found to be needed for viral cell entry with severe acute respiratory syndrome coronavirus (SARS; Huang et al., 2006; Simmons et al., 2005). Cathepsin L generates kinins from LMWK and HMWK at the infection site (Desmazes, Gauthier, & Lalmanach, 2001), thus acting as a

kininogenase independently of kallikreins, which are unable to generate kinins under inflammatory conditions to restore kinin levels (Desmazes, Galineau, Gauthier, Brömme, & Lalmanach, 2003). Interestingly, cathepsin L exhibits hypotensive effects with increase in bradykinin release from kininogen in vivo, due to its kininogenase activity (Puzer et al., 2005). SARS-COV-2-related effects on cathepsin L activity may modulate kinin and especially bradykinin levels, which may be at least partly responsible for some clinical aspects, supporting KKS role in COVID-19 pathogenesis (Johnson et al., 2009). This is supported by previous studies reporting an increase in the risk of ARDS with increase in angiotensin II and decrease in angiotensin 1–7 (Kuba et al., 2005). Also, enhancing the effects of angiotensin 1–7 has been reported as likely to provide protection from ARDS induced by coronaviruses (Imai et al., 2005).

Moreover, suppressed eNOS and NO deficiency are associated in COVID-19 patients with endothelial dysfunction leading to thrombotic events and organ dysfunctions (Green, 2020; Varga et al., 2020), thus supporting the hypotheses of deleterious suppressed B2R stimulation (which stimulate eNOS) and depressed NO synthesis.

All ACE2 inhibition effects were observed in COVID-19 patients who exhibit increased risk of vasoconstriction (Ruocco, Feola, & Palazzuoli, 2020), proinflammatory cytokine profile (Jamilloux et al., 2020), acute phase reactants including C-reactive protein (Liu et al., 2020), pulmonary fibrosis (Spagnolo et al., 2020), coagulopathy with elevated plasma D-dimer, pulmonary thrombosis and venous thromboembolic events (Frater, Zini, D'Onofrio, & Rogers, 2020; Thachil, 2020), disseminated intravascular coagulation (Lillicrap, 2020) and ARDS (Gattinoni, Chiumello, & Rossi, 2020; Jamilloux et al., 2020).

6 | CURRENTLY PROPOSED ANTI-COVID-19 THERAPIES AIMING TO MODULATE RAS AND KKS

Many drugs have been used and thousands of clinical trials started to investigate the benefits of anti-COVID-19 therapies (Esposito, Noviello, & Pagliano, 2020). Of these, drugs theoretically effective in modulating the RAS and KKS are currently being trialed to alleviate the consequences of ACE2 downregulation. Some drugs target ACE2 activity, while most target consequential effects of ACE2 inhibition mainly regarding the RAS. Surprisingly, none considered the strong functional relationships between RAS and KKS and the influence of ACE2 inhibition on both systems.

Some studies recommended targeting ACE2 itself to competitively antagonize SARS-COV-2 binding (e.g., using soluble receptor-binding domains or antibodies). ACE2 blockers may be useful during the initial phase of infection or as prophylaxis to inhibit SARS-COV-2 entry (Kruse, 2020). Meanwhile, ACE2 blockage may exacerbate COVID-19 severity by exaggerating the consequences of ACE2 inhibition; accordingly, even its usage as prophylaxis may lead to ACE2 inhibition manifestations. Interestingly, one pilot study recommended restoring ACE2 downregulation by using recombinant human ACE2

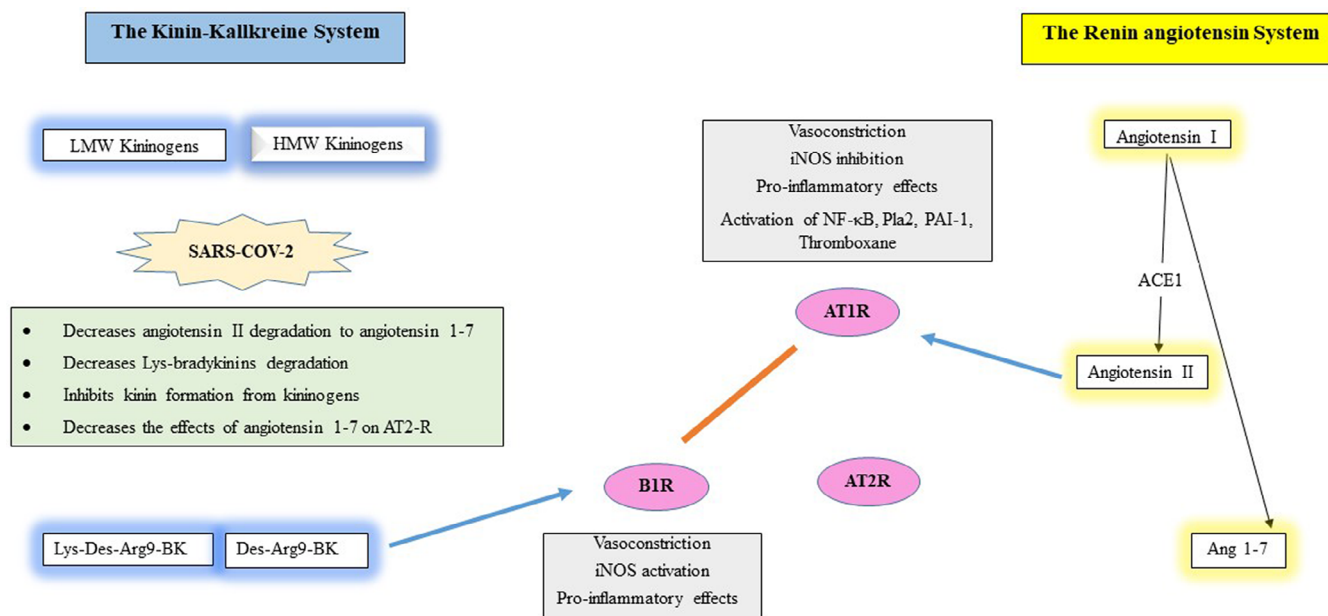


FIGURE 2 The pathophysiological effects of SARS-CoV-2 on both the renin-angiotensin and KKSs

(rhACE2, GSK2586881) aiming at decreasing angiotensin II and increasing angiotensin 1–7, but no improvement in physiological or clinical parameters was observed (Peng et al., 2013).

Other studies recommended angiotensin receptor blockers to block angiotensin II overactivation effects (Gurwitz, 2020; Silhol et al., 2020), neglecting the effects of ACE2 inhibition on the KKS. Although classical ACE inhibitors do not inhibit ACE2 (Zisman, 2005), some studies recommended ACE inhibitor use to decrease angiotensin II overexpression. These studies depended on observations of clinical improvements in COVID-19 patients on antihypertensive ACE inhibitors evident by the lower prevalence of severe presentations, reduced hospitalization risk, lower viral load and plasma IL-6 and increased CD3 and CD8 T-cell counts (Khera et al., 2020; Meng et al., 2020). A meta-analysis suggested that ACE inhibitors may reduce mortality (Ghosal, Mukherjee, Sinha, & Gangopadhyay, 2020), consistent with the association with reduced mortality in septic patients (Hsu et al., 2020). By contrast, other studies discouraged its use as possibly facilitating SARS-CoV-2 entrance into the cell (Gurwitz, 2020; Hoffmann et al., 2020) and leading to bradykinin escape (Ruocco et al., 2020). Although ACE inhibitor therapy was associated with decreased Th1/Th2 cytokine ratios and inflammatory cytokine production, no inhibition of ACE2 was observed (Gage et al., 2004). Additionally, ACE inhibition may prevent bradykinin inhibition leading to the accumulation of Lys des-Arg9-bradykinin and des-Arg9-bradykinin (ACE2-related reduced degradation), resulting in B1R overstimulation and detrimental clinical effects.

Icatibant, a selective peptidomimetic B2R antagonist of 10 amino acids, was proposed as useful drug to alleviate the inflammatory symptoms by inhibiting B2R effects and consequently angiotensin II/AT1R actions (van de Veerdonk et al., 2020). This hypothesis was

based on the functional relationships between AT1R and B2R, although AT1R/B2R heterodimer formation is controversial (Abdalla, Lother, el Massiery, & Quitterer, 2001). Arachidonic acid can inactivate SARS-CoV-2 as its eicosanoids metabolites may help in resolution of inflammation and regulate the phagocytic action of macrophage and other immunocytes (Das, 2020). Current laboratory data obtained in COVID-19 cases (increased eicosanoids) contradict the hypothetical basis for this therapy. Interestingly, antagonistic maneuvers directed against some consequences of angiotensin II overexpression have been recommended. Of these, corticosteroids have been evaluated as a potent treatment to inhibit cytokine production by NF-κB-mediated transcription factor inhibition (Qin et al., 2020; Russell, Millar, & Baillie, 2020). Anticoagulants such as heparin have been suggested to reduce mortality (Thachil, 2020). Although these studies did not cover all SARS-CoV-2-induced pathological effects, they may be beneficial against specific consequences such as thrombosis and thromboembolic events, thus ameliorating COVID-19 severity.

Inhaled NO with its potential vasodilatory and bronchodilatory properties is also currently being investigated aiming to decrease pulmonary hypertension, improve arterial oxygenation and reduce spread and density of lung infiltrates in COVID-19 patients (Chen et al., 2004). Interestingly, NO has been shown able to inactivate viral replication in vitro by modifying proteins and nucleic acids (Croen, 1993) with many viruses (Klingström et al., 2006; Saura et al., 1999) including SARS coronavirus (Åkerström, Gunalan, Keng, Tan, & Mirazimi, 2009). Theoretically, this therapy is appealing as deficient NO bioavailability is associated with endothelial dysfunction (Tomasian, 2000). Deficient NO bioavailability may result from reduced NO production by eNOS which occurs from decreased B2R and AT2R stimulation and/or ROS-related increased NO breakdown

which increases with ATIR and B1R stimulation (Taddei, Ghiadoni, Viridis, Versari, & Salvetti, 2003).

Teicoplanin and glycopeptides have also been proposed to treat COVID-19 patients by targeting cathepsin L in the late endosomes and thus blocking the virus replication cycle (Zhang et al., 2020). Targeting cathepsin L may be useful as a prophylactic strategy to prevent SARS-CoV-2 entry into the cells and/or limit the subsequent COVID-19 severity before host defense impairment as observed with influenza A (Xu, Greenland, Gotts, Matthay, & Caughey, 2016). However, this targeting strategy may also aggravate COVID-19 severity as cathepsin L plays a crucial pathogenic role by modulating bradykinin levels.

Interestingly, a new potential therapeutic approach to combat COVID-19 by using Rho kinase inhibitors such as fasudil has been suggested (Abedi, Rezaee, & Karimi, 2020), as it showed a protective effect from lung injury through its ability to counteract the proinflammatory and immune responses of Rho kinase that mediates lung injury. Rho kinase inhibitors also shown to have antifibrotic effects and ability to upregulate ACE2 (Abedi, Hayes, Reiter, & Karimi, 2020; Zhang, Penninger, Li, Zhong, & Slutsky, 2020). This is consistent with other studies that showed that Rho pathway is activated by angiotensin II/AT1R (Kimura & Eguchi, 2009; Suzuki et al., 2009).

7 | SNAKE VENOM-DERIVED PEPTIDES

Snake venoms contain a mixture of amino acids, proteins, peptides, nucleotides, lipids, carbohydrates and metallic elements coupled to proteins (Calvete, Juárez, & Sanz, 2007; Georgieva, Arni, & Betzel, 2008). Although these components may be lethal, they constitute a rich biological resource of significant therapeutic value including promising antiviral drugs (Kang et al., 2011; Meenakshisundaram, Sweni, & Thirumalaikolundusubramanian, 2009; Pennington, Czerwinski, & Norton, 2018; Rivero et al., 2011). Several studies reported that snake venom components have antiviral activity against measles, Sendai, dengue, yellow fever and human immunodeficiency viruses (Borkow & Ovadia, 1999; Meenakshisundaram et al., 2009; Muller et al., 2012). Snake venom properties may constitute promising therapeutic options against defense mechanisms developed by viruses (Meenakshisundaram et al., 2009).

Interestingly, the venom-derived peptides present properties adequate to counteract COVID-19 consequences in the light of SARS-CoV-2-related pathophysiological mechanisms. BPPs, isolated from *Bothrops jararaca* venom (Ferreira, Greene, Alabaster, Bakhle, & Vane, 1970), launched the discovery of bradykinin in the bitten patients (e Silva, Beraldo, & Rosenfeld, 1949), allowing understanding of the physiological roles of the KKS (Linz, Wiemer, Gohlke, Unger, & Schölkens, 1995). Peptide fraction analysis of *Bothrops jararaca* venoms contains various BPPs (9a, 10b, 10c, 11a, 11d, 11e, 12b, 12c, 13a, 13b, 14a), short proline-rich peptides with remarkable functional differences (Camargo, Ianzer, Guerreiro, & Serrano, 2012; Morais et al., 2011). The first BBP to be sequenced was Pyr-Lys-Trp-Ala-Pro-OH (Munawar et al., 2016).

BPP-10c (Glu-Asn-Trp-Pro-His-Pro-Gln-Ile-Pro-Pro) strongly decreases angiotensin II by inhibiting ACE, increasing bradykinin-related effects on B2R, increasing NO-attributed antioxidant, antiinflammatory and neuroprotective effects and exhibiting direct neural antihypertensive effects. Therefore, we hypothesized that BPP-10c may be an excellent anti-COVID-19 treatment due to its ability to counteract most of the deleterious effects of SARS-CoV-2 on both RAS and KKS.

BPPs increase bradykinin-induced hypotension and decrease angiotensin I-related vasopressor effects by inhibiting ACE (Camargo et al., 2012; Lopes et al., 2014). They represent the first natural bradykinin agonists and ACE inhibitors (Camargo et al., 2012). BPPs augment bradykinin-related effects by interacting directly on bradykinin receptors rather than inhibiting bradykinin degradation by ACE1 inhibition (Chi et al., 1985). BPP-10c strongly potentiates bradykinin-related effects on B2R and is additionally a strong selective ACE C-domain inhibitor (400-fold more selective than for the N-domain; Camargo et al., 2012; Cotton et al., 2002). Angiotensin I is predominantly hydrolyzed by the C-domain, whereas bradykinin is hydrolyzed by both active domains (Junot et al., 2001). Hence, a purely C-domain selective inhibitor would be more beneficial as it mainly decreases angiotensin II by inhibiting its synthesis from angiotensin I by the C-domain. BPPs only decrease bradykinin degradation while preventing its accumulation by preserving ACE N-domain activity (Messerli & Nussberger, 2000). This property renders BPPs superior to classical ACE inhibitors that have the risk of developing bradykinin-mediated angioedema. Besides its ability to inhibit ACE and directly activate bradykinin-B2R, BPP-10c exerts its antihypertensive effect by increasing free intracellular calcium in neuronal cells and releasing specific neurotransmitters in the central nervous system (Lameu et al., 2010; Querobino, Ribeiro, & Alberto-Silva, 2018).

Additionally, BPP-10c is reported to enhance argininosuccinate synthetase (AsS) activity leading to sustained increase in NO production (Camargo et al., 2012; Morais et al., 2011, 2013). BPP-10c binding to AsS enhances adenosine triphosphate and citrulline (Guerreiro et al., 2009) leading to NO release from endothelial cells and vasodilatation (Morais et al., 2013). AsS enhances argininosuccinate synthesis via conjugation of aspartate with citrulline. Argininosuccinate is cleaved by argininosuccinate lyase resulting in fumarate and L-arginine formation (Haines, Pendleton, & Eichler, 2011). This amino acid participates in the synthesis of neuroprotective molecules including agmatine and various polyamines such as spermine, spermidine and putrescine (Blantz, Satriano, Gabbai, & Kelly, 2000; Querobino et al., 2018). Polyamines could prevent alterations in mitochondrial membrane permeability, regulating calcium concentrations and NOS activity (Jamwal & Kumar, 2016). Agmatine is reported to exhibit antiinflammatory properties by inhibiting NF- κ B leading to iNOS suppression (Ahn et al., 2012), inhibiting TNF- α (Hong, Kim, Lee, & Seong, 2009) and inducing neuroprotective and antioxidant actions (Freitas et al., 2016). L-arginine can also be metabolized to NO (Maes, Galecki, Chang, & Berk, 2011). The importance of the arginine-citrulline cycle for endothelial NO production was supported by a

report of two infants with a deficiency of argininosuccinate lyase, who were shown to be hypertensive (Fakler, Kaftan, & Nelin, 1995).

BPP-10c reduces ROS production (Querobino et al., 2018; Zhou, Ai, Chen, & Li, 2019), increases NO synthesis (de Oliveira et al., 2010), reduces NF- κ B expression and reduces iNOS expression (Querobino et al., 2018). BPP-10c has been reported to be safe and without cytotoxic effects (Querobino et al., 2018). It caused sustained reduction in blood pressure in hypertensive but not normotensive rats (Guerreiro et al., 2009). Other studies recommended its consideration as a potential therapeutic agent for various diseases related to NO deficiency (Morais et al., 2011).

8 | CONCLUSION

SARS-COV-2 downregulates ACE2 and affects cathepsin L that significantly contributes to COVID-19 pathophysiology by increasing the proinflammatory and organodestructive effects of angiotensin II and Lys-bradykinins and decreasing the antiinflammatory and organoprotective effects of angiotensin 1–7, NO and bradykinin. Most investigations on anti-COVID-19 therapies did not consider the effects on both RAS and KKS. Snake venom-derived BPP-10c exhibits remarkable organoprotective effects targeting both systems and thus providing great value as a natural treatment option to alleviate COVID-19 manifestations. Further trials are now required to evaluate any clinical benefits.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Ahmed S. Gouda: Writing – original draft (lead); writing – approval.

Bruno Mégarbane: Writing – original draft (lead); writing – approval.

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