MINI-REVIEW

The Pathophysiology of COVID-19 and SARS-CoV-2 Infection

Kinins and chymase: the forgotten components of the renin-angiotensin system and their implications in COVID-19 disease

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Abstract

The unique clinical features of COVID-19 disease present a formidable challenge in the understanding of its pathogenesis. Within a very short time, our knowledge regarding basic physiological pathways that participate in SARS-CoV-2 invasion and subsequent organ damage have been dramatically expanded. In particular, we now better understand the complexity of the renin-angiotensin-aldosterone system (RAAS) and the important role of angiotensin converting enzyme (ACE)-2 in viral binding. Furthermore, the critical role of its major product, angiotensin (Ang)-I (1–7), in maintaining microcirculatory balance and in the control of activated proinflammatory and procoagulant pathways, generated in this disease, have been largely clarified. The kallikrein-bradykinin (BK) system and chymase are intensively interwoven with RAAS through many pathways with complex reciprocal interactions. Yet, so far, very little attention has been paid to a possible role of these physiological pathways in the pathogenesis of COVID-19 disease, even though BK and chymase exert many physiological changes characteristic to this disorder. Herein, we outline the current knowledge regarding the reciprocal interactions of RAAS, BK, and chymase that are probably turned-on in COVID-19 disease and participate in its clinical features. Interventions affecting these systems, such as the inhibition of chymase or blocking BKB1R/BKB2R, might be explored as potential novel therapeutic strategies in this devastating disorder.

ACE2; bradykinin; chymase; COVID-19; SARS-CoV-2

INTRODUCTION

One of the rewarding scientific consequences of the COVID-19 pandemic is the renewed interest in the renin-angiotensin-aldosterone system (RAAS), an endocrine axis whose pivotal role in the regulation of blood pressure, fluid homeostasis, renal function, coagulation, inflammation, fibrosis, and function of various vital organ has been elucidated during the past century (1, 2). The classical RAAS consists of renin, a protease secreted by granular cells localized to renal glomerular afferent arterioles and produces angiotensin (Ang) I, an inactive 10 amino acid (aa) peptide from a circulating precursor termed angiotensinogen. Ang I is then converted by angiotensin-converting enzyme (ACE) to Ang II, an 8 aa active peptide. Ang II is the main effector component of the RAAS, as evident by its potent vasoconstrictive, sodium-retaining, proinflammatory, and profibrotic actions (Fig. 1). In light of its unequivocal harmful involvement in the pathogenesis of various cardiovascular and renal diseases, ACE inhibitors (ACE-Is) and Ang II receptor blockers (ARBs) have been developed and extensively used in patients with hypertension, heart failure, and chronic kidney disease (3). Fortuitously, the recent two decades have witnessed elucidation of the RAAS, with the identification of new components of this hormonal system, namely ACE2, Ang 1–7, and MasR, a G protein-coupled Ang 1–7 receptor (Mas) (4–8) (Fig. 1). Initially, ACE2 had been identified in the testis. However, it was later found to be expressed in various vital organs including the heart, kidney, lung, liver, small intestine, brain, and vasculature (6, 9, 10). ACE2 is a zinc membranal single-pass metalloenzyme, with an extracellular active domain that converts Ang I into Ang 1–9 and in turn to Ang 1–7 by ACE (4–8). Moreover, ACE2 can directly convert Ang II to Ang 1–7, having a 400-fold higher affinity to Ang II as compared with the classic ACE (2). In addition, pathway for Ang 1–7 generation, shown in Fig. 1, involves neural endopeptidase-neprilysin (NEP), which converts Ang I directly into Ang 1–7 (2). In contrast to Ang II, Ang 1–7 exerts vasodilatory, antiproliferative, anticoagulant, and antifibrotic activity, via its specific Mas-
receptor (MasR), thus counterbalancing the adverse effects of Ang II mediated by ATIR (4, 6, 8, 9, 11).

The well-explored kinin-kallikrein system (KKS) and its numerous and compound interactions with the RAAS (12) has so far been largely ignored and underestimated, especially its potential role in the clinical manifestations of COVID-19. The principal active representatives of the kinin system are bradykinin (BK) and its metabolite [des-Arg9]-BK, a 9 aa peptide produced by the serine protease kallikrein from inactive circulating or tissue-bound preproprotein kininogen or from BK by ACE, acts on target organs via BKB-1R, where it induces in

Angiotensin I (Ang I) is converted by angiotensin-converting enzyme (ACE) to Ang II, the main vasoconstrictor, sodium-retaining, proinflammatory, and profibrotic effector of RAAS. Recently, new components of RAAS, namely, ACE2, Ang-(1–7) and its Mas-receptor (MasR), were identified. ACE2 converts Ang I into Ang-(1–9), and in turn to Ang-(1–7) by ACE. Moreover, ACE2 can directly convert Ang II to Ang-(1–7). Additional pathway for Ang-(1–7) involves neural endopeptidase-nephrilysin (NEP), which converts Ang I directly into Ang-(1–7). In contrast to Ang II, Ang-(1–7) exerts vasodilatory, antiproliferative, and antifibrotic activity, via MasR, thus counterbalancing the adverse effects of Ang II mediated by ATIR. The right side of the scheme describes bradykinin (BK) synthesis from kininogen, a process mediated by kallikreins. BK acts via BKB-2R, where it induces vasodilation, natriuresis, antithrombosis, pain, and chymase upregulation. BK is metabolized into inactive metabolites by kininase. In addition, [des-Arg9]-BK, a 9 aa peptide produced by the serine protease kallikrein from inactive circulating or tissue-bound preproprotein kininogen or from BK by ACE, acts on target organs via BKB-1R, where it induces inflammation, coagulation, and pain. SARS-CoV-2 infection downregulates ACE2 and eventually generates Ang-(1–7) depletion, leading to unopposed vasoconstriction and inflammation. In addition, ACE2 downregulation by SARS-CoV-2 infection upregulates [des-Arg9]-BK, thus aggravating its inflammatory and coagulopathy actions. Furthermore, depletion of Ang-(1–7) characterizing patients with COVID-19 likely enhances BK degradation into inactive metabolites, but still associated with [des-Arg9]-BK levels due to ACE2 depletion, thus aggravating the deleterious effects mediated by BKB-1R. Chymase, expressed in different cell types, including mast cells, cardiac fibroblasts, and vascular endothelial cells, is a major non-ACE of tissue Ang II generation from Ang-(1–12) and Ang I, especially in the heart and blood vessels. Chymase also activates transforming growth factor-β (TGF-β) and matrix metalloproteinase (MMP-9) by converting their precursors into active forms, involved in tissue inflammation and fibrosis, leading to structural injury and organ remodeling as well as enhanced coagulation.
not by ARBs (26, 27). NEP also has direct critical regulating functions involving BK, Ang I and Ang II (28). Furthermore, ACE2 hydrolyzes [des-Arg9]-BK to biologically inactive breakdown products (2), whereas Ang 1–7 prevents BK degradation, thus may potentiate its effects (Fig. 1). In summary, the generation, action, degradation, and elimination of BK is linked to RAAS. Moreover, the interplay between these two systems suggests a potential role for BK in COVID-19 hyperinflammation (29), as summarized in the following section (THE KININ-KALLIKREIN SYSTEM AND COVID-19 DISEASE).

THE KININ-KALLIKREIN SYSTEM AND COVID-19 DISEASE

The involvement of the kinin-kallikrein system in the pathogenesis of COVID-19 manifestations has not yet received appropriate attention despite being tightly linked to RAAS, which is markedly involved in SARS-CoV-2 infection and organ damage (30). Specifically, the SARS-CoV-2 viral spike glycoprotein binds with high affinity to ACE2, where it triggers its internalization along with the virus (10, 30–33). This is of relevance to pulmonary, cardiac, and renal tissues of infected subjects, especially patients with heart failure, diabetes, pulmonary diseases, and hypertension, clinical settings characterized by intense upregulation of ACE2 (34, 35). In a vicious feed-forward cycle, binding and intracellular translocation of SARS-CoV-2, coupled with ACE2, leads to ACE2 depletion and loss of its endogenous normal enzymatic function, with depletion of its catalytic product, Ang 1–7, resulting in elimination of its beneficial effects (Fig. 1). Ang 1–7, acting through MasR, is necessary for maintaining the integrity of crucial cell types and organ systems, which are known to be principally affected in the pathophysiology of COVID-19 disease, including pulmonary alveolar cells and macrophages, vasculature, cardiovascular, gastrointestinal, and renal tissues. Although the physiology and pathophysi-ology of both ACE/Ang II/AT1R and ACE2/Ang-1-7/MasR systems in COVID-19 disease have already been studied since the epidemic outbreak, only limited attention has been directed to the potential involvement of the kinin-kallikrein in the pathogenesis of this disease (25).

Considering the proinflammatory and proliferative actions of BK along enhanced leakage of blood vessels and edema formation as well as the induction of pain and general fatigue (23, 24), hallmark features of COVID-19 disease, it is tempting to assume that BK/BKB-1R/BKB-2R and RAAS interplay is deeply involved in the pathogenesis of this disease. In this context, it is conceivable that ACE2 depletion, characterizing SARS-CoV-2 infection, enhances [des-Arg9]-BK levels, promoting inflammation and coagulopathy via BKB-1R (Fig. 1) (20, 30). Previous studies in ACE2-deficient mice showed that loss of ACE2 function in the lung leads to worsening of inflammation induced by acid aspiration or lipopolysaccharide (LPS) (36, 37). Until recently, little was known about how inflammatory stimuli affect ACE2 function in the lung (38). Fortunately, Sodhi et al. (39) demonstrated that ACE2 enzymatic activity was reduced over time following LPS delivery to the mouse lung, most likely due to downregulation of its expression and abundance in pulmonary tissues. Moreover, these authors reported that lack of functional ACE2 in ACE2−/− mice resulted in increased recruitment of neutrophils to the lung in the setting of LPS challenge, along with intensification of lung inflammation and injury. This pattern is partially attributed to [des-Arg9]-BK and BKB-1R-mediated release of proinflammatory chemokines, such as C-X-C motif chemokine 5 (CXCL5), macrophage inflammatory protein-2 (MIP2), and tumor necrosis factor-α (TNF-α) from airway epithelia (39). Moreover, activation of BKB-1R by [des-Arg9]-BK resulted in vasoconstriction of isolated pig coronary arteries, following the induction of this BK receptor subtype by endotoxin (40). In addition, BKB-1R is upregulated in response to stress such as ischemia/reperfusion injury, chronic inflammation, and diabetes (41, 42).

These experimental studies suggest additional direct link-ages between ACE2 depletion and accumulation of [des-Arg9]-BK, which activates the BKB-1R axis and eventually augments LPS-induced neutrophil infiltration in the pulmonary tissues. Collectively, there is ample evidence suggesting that ACE2 depletion triggered by SARS-CoV-2 leads to enhanced BKB-1R-mediated signal, conceivably manifested by the clinical picture. However, ACE can convert BK into BK1-5 that has thrombin inhibitory action, supporting anticoagulatory action of BK probably via NO and prostacyclin production and release of tissue plasminogen activator (13). Moreover, kallikrein is a kinetically favorable activator of single-chain urokinase. Considering the established role of BK as a hypotensive peptide, it appears that the plasma KKS serves as a physiological counterbalance to the hypertensive prothrombotic RAAS (13).

Noteworthy, reciprocal interactions may occur as well, with BK affecting RAAS. Indeed, BK activates ADAM17 via BKB-2R (43) and [des-Arg9]-BK activates matrix metalloprotease (MMP) via BKB-1R (44, 45), eventually leading to the shedding of ACE2 from cell membranes. This may accelerate the depletion of ACE2 and Ang 1–7, on top of ACE2 internalization and degradation, caused by SARS-CoV-2 infection. Clinical evidence for potential involvement of the kinin-kallikrein system in COVID-19 manifestations arises from an elegant though controversial study by Garvin et al. (46). This work, conducted in Wuhan, People’s Republic of China, describes changes in “gene expression” in cells in bronchoalveolar lavage fluid (BALF), obtained from nine patients with COVID-19. Interestingly, BALF from these patients displayed an extraordinarily imbalanced RAAS as was evident by decreased expression of ACE (−eightfold), combined with a 199-fold increases in ACE2, that presumably increases pulmonary BK levels. In addition, Garvin reported an upregulation of BKB-2R (207-fold) and BKB-1R (2,945-fold), possibly leading to pain, vasodilation, and microvascular leakage, with pulmonary inflammation and noncardiogenic congestion. According to these authors, BK-mediated leakage was associated with excess formation of hyaluronic acid, enhancing the formation of a viscous hydrogel that interferes with pulmonary gas exchange in patients severely affected by COVID-19. The involvement of the BK system in pulmonary manifestations of COVID-19 (“Bradykinin storm” as termed by the authors) is further supported by their findings that the BALF of infected patients exhibited upregulation of pulmonary BK-related genes, such as the BK precursor, most enzymes that degrade BK, and BK1-9 and BK1-8. Garvin et al. (46) also examined transcriptional changes in the hemo-
static and complement systems. Interestingly, FXII was inhibited (–33-fold), which inhibits FXII—was downregulated substantially, leading to further increases in BK in patients with COVID-19, given its role in the activation of kallikrein gene (KLKB1) (47). Noteworthy, KLKB1 is activated by FXII of the intrinsic coagulation pathway, which is normally kept in check by the Ci-inhibitor encoded by SERPING1. This could lead to an important ancillary effect of inhibiting the feedback loop of FXII activation by kallikrein (11, 48). Collectively, Garvin et al. (46) attributed most of the features of COVID-19 disease to shift of the entire RAAS to produce Ang–1–12, to an upregulation of AT1R and AT2R (430- and 177-folds, respectively), along with the activation of the kinin-kallikrein system. The enhanced pulmonary BK system expression in BALF of patients with COVID-19 shown by Garvin et al. (46) may explain the virulence of COVID-19 in hypertensive elderly patients treated with ACE-Is. In this setup, ACE-Is may upregulate ACE2 expression, providing an ideal environment for SARS-CoV-2 attachment to target cells, enhancing viral invasion with a consequent malignant inflammatory response stimulated by increasing BK levels including [des-Arg9]-BK (49). In contrast, the low levels of ACE2 and BK in children might explain the lower morbidity and mortality in the pediatric population, in line with these concepts. Furthermore, an exploratory randomized clinical trial by van de Veerdonk et al. (50) found that administration of icatibant (BKB-2R antagonist) temporarily improved total RNA in inflammatory cells, and may not truly affect changes in cell population in the BALF. In addition, high levels of BK should down-regulate BKB-1R and BKB-2R receptors subtypes, which is not the case in this study, suggesting that high mRNA expression does not always parallel immunoreactivity. Last, the observed intensified expression of ACE2 transcription contradicts the currently adopted concept of ACE2 depletion during SARS-CoV infection, underscoring the need for additional confirmatory studies. Yet, one may not exclude increased soluble ACE2 levels along with decreased membranal ACE2 in patients with COVID-19.

### CHYMASE AND COVID-19

As illustrated in Fig. 1, an alternative pathway of the conversion of Ang–1–12 (generated from angiotensinogen by a nonrenin pathway) into Ang II takes place by the proteolytic enzyme, chymase. Chymase (EC 3.4.21.39), a chymotrypsin-like enzyme, can also directly cleave Ang I into Ang II (54), thus contributing to the formation of Ang II from either Ang–1–12 or Ang I (55, 56). This explains the ongoing generation of Ang II in patients on ACE-Is (57) and adds uncertainty to the widely believed assumption that these inhibitors suppress the deleterious effects of Ang II by inhibiting locally generated Ang II (58). Chymase is expressed in different cell types, including mast cells, cardiac fibroblasts, and vascular endothelial cells (59, 60), where it provides the major source of tissue Ang II generation, especially in the heart (60, 61), and to a lesser extent in the vascular wall (54). Therefore, the physiologic role of the Ang–1–12 /chymase/Ang II pathway should be acknowledged, besides two other well-known pathways, namely, ACE/Ang II/AT1R and ACE2/Ang1-7/MasR. Chymase also activates transforming growth factor-β (TGF-β) and MMP-9 by converting their precursors into active forms, involved in tissue inflammation and fibrosis, leading to structural injury and organ remodeling (62). In this regard, previous studies indicated that chymase is involved in the pathogenesis of chronic cardiac and pulmonary inflammation and fibrosis (63). Furthermore, chymase activates and catalyzes degradation of thrombin and plasmin, thus playing an important role in the regulation of coagulation (54). Proteolysis of thrombin and plasmin in the vascular wall is mediated by chymase-heparan proteoglycan complexes expressed by mast cells, binding thrombin and plasmin through its heparin-binding domains (54). Therefore, by affecting remodeling of extracellular matrix and coagulation processes, chymase might be important in the pathogenesis of cardiovascular diseases and coagulopathy. The conversion of Ang–1–12 into Ang II by chymase further plays a deleterious role in target organ remodeling and in augmenting cardiac and vascular contractility via AT1R (64, 65). Thus, local chymase-mediated generation of Ang II, unrelated to the circulatory RAAS, explains the lack of effect of ARBs and ACE-Is on cardiac Ang II content (58, 66, 67). Chymase is a major player in cardiac remodeling, characterizing heart failure, probably via Ang–1–12/chymase/Ang II or Ang I/chymase/Ang II trails (68). Furthermore, chymase-mediated generation of Ang II from Ang–1–12 was suggested to be involved in the inotropic, contractile, and proarrhythmic effects of Ang II in experimental and clinical heart failure (69, 70). Indeed, chronic inhibition of chymase was found to prevent cardiac fibrosis and improved diastolic...
dysfunction in a model of progressive heart failure in dogs (71). Interestingly, combined inhibition of both chymase and ACE was superior to ACE-I alone, as was evident by improved cardiac function and cardiac remodeling in rodents (58). In line with these findings, clinical studies demonstrated that an inhibitor of chymase-specific RNA aptamer improved cardiac function in patients following myocardial infarction (72).

In contrast to ACE, chymase mediates the generation of Ang II without affecting BK degradation (60) and probably ACE2 expression. Yet, an interplay exists between chymase and the kinin-kallikrein system, as was demonstrated experimentally in vivo (58, 73). Specifically, chronic administration of ACE-I increased BK levels in mice, along with enhanced activity of myocardial chymase and accelerated formation of Ang II, effects prevented by Hoe140, a BKB-2R antagonist (58). These observations might be at odds with the concept that BK provides the well-established beneficial effects of chronic ACE inhibition, despite its proinflammatory detrimental role via BKB-1R (74). Thus, BK induces the release of chymase, which may help maintaining Ang II levels, actually being detrimental rather than beneficial (75). On the other hand, ACE inhibition increases ACE2 expression and Ang-1–7 (76), which, via Ang-1–7/MasR axis, impairs BK degradation (possibly through competition with Ang I on ACE) (73, 77), thus contributing to consequent vasodilation. Moreover, Ang-1–7 and AVE0991 (a MasR agonist) exhibit a favorable kinetic of NO release by endothelial cells (78).

Although the involvement of chymase-dependent generation of Ang II in COVID-19 disease remains to be determined, one may assume that in light of the inflammatory and procoagulant nature of COVID-19 disease, chymase may be a potential mediator, divulging an additional potential therapeutic target for COVID-19 disease. Support for this assumption is derived from Garvin et al. (46), who outlined stimulatory effects of SARS-CoV-2 on BK system in patients with COVID-19 and the positive interplay between BK and chymase (58). The findings that ACE-I enhanced BK production, along enhanced activity of myocardial chymase and accelerated formation of Ang II and TGF-β (57, 62), could be of relevance to the debatable matter of ACE-I and ARBs use in COVID-19 subjects. Although ACE-Is and ARBs could affect SARS-CoV-2 infectivity and COVID-19 disease progression by enhancement of ACE2 expression, so far there is no keen evidence that these drugs adversely affect SARS-CoV-2-induced acute lung injury (76). Therefore, it is appealing to assume that upregulation of chymase in cardiovascular diseases (71, 79, 80) may explain both the moderate impact of ACE-I on clinical cardiovascular end points in patients with congestive heart failure (CHF) (81) and potential deleterious effects of RAAS blockers in patients with COVID-19 (76, 82, 83). However, there is no consensus whether ACE-Is and ARBs have distinct impact on the morbidity and mortality of patients with COVID-19, as the reported results are heterogeneous probably due to the lack of prospective studies (76, 82, 83). In summary, chymase inhibitors may emerge as a sensible strategy for mitigating the adverse effects of Ang II and TGF-β in COVID-19, probably without the need of classic RAAS blockers, although further studies are needed to explore this idea.

**PERSPECTIVES AND CONCLUSIONS**

COVID-19 is characterized by vital multiorgan derangement as evident by respiratory distress, cardiac dysfunction, kidney injury, and coagulopathy. These complications are largely attributed to the fact that SARS-CoV-2 uses ACE2 for target cell invasion, leading to neutralization of its advantageous MasR-mediated effects, especially in patients with background diseases such as diabetes, heart, and renal failure. Yet, the intensive focus on the ACE/Ang II/AT1R and ACE2/Ang-I–7/MasR imbalance deflected the attention from two additional major components of the RAAS, namely, kinin-kallikrein and chymase. These relatively undervalued factors may turn out to be major participants in the pathogenesis of COVID-19 disease, as both exert proinflammatory and procoagulant effects via AT1R and BKB-1R, respectively. In light of their deleterious actions in vital organs, including the vasculature, lung, and heart, inhibitors of both chymase and BK may potentially be used in the management of COVID-19 disease. Moreover, as ACE-I probably aggravate COVID-19 manifestations with BK upregulation and imbalanced Ang species (84), chymase inhibitors may be a good option for attenuating the adverse effects of unleashed RAAS during SARS-CoV-2 infection, as they impair Ang II generation without paying the undesired price of ACE-I-induced BK augmentation. In addition, ACE2 depletion during COVID-19 likely contributes to the pathogenesis of lung inflammation, in part because of the impaired ability to inhibit des-Arg9-BK/BKB-1R axis, resulting in intensified inflammation in pulmonary tissues. In summary, our theory extends that of Roche and Roche (25) and emphasizes the contribution of BK and chymase in the pathogenesis of COVID-19 disease and suggests potential new therapeutic maneuvers based on chymase inhibitors (fulacimstat), on selective BKB-2R blockers, such as icatibant, or inhibitors of BK synthesis, such as ecallantide, used for the management of hereditary angioedema flares.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

Z.A., D.B.H-G., and S.N.H. prepared figures; Z.A., K.S., D.B.H-G., E.K.-D., and S.N.H. drafted manuscript; Z.A., K.S., D.B.H-G., E.K.-D., and S.N.H. edited and revised manuscript; Z.A., K.S., D.B.H-G., E.K.-D., and S.N.H. approved final version of manuscript.

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