Counters-Regulatory Renin-Angiotensin System: An Important Line of Research to Understand and Limit the Severity of COVID-19

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Recent evidence on inefficacy and poor tolerance of (hydroxy)chloroquine as a therapeutic option for COVID-19 gives rise to less toxic treatment research for COVID-19. An attractive line of research relies on the renin-angiotensin system (RAS), the role of which is largely highlighted during the COVID-19 pandemic [1, 2]. SARS-CoV-2 interferes with RAS through interactions between its spike glycoprotein and the Angiotensin-Converting Enzyme 2 (ACE2) receptor [3, 4], which is exposed on the surface of multiple endothelial and epithelial cell types. The resulting RAS overreaction is thought to be at the origin of some of COVID-19 poor-prognosis outcomes, including kidney, cardiac, vascular, and immune dysfunctions, notably the serious cytokine storm resulting in acute respiratory distress syndrome [1]. A recent report suggests that RAS inhibitors may modulate the severity of viral infection and mortality risk in COVID-19 patients [2]. In this respect, targeting RAS by using candidate chemotherapeutic drugs stands out as a relevant line of research for COVID-19 treatment. The proposed molecules are, up to now, ACE inhibitors (to prevent the production of angiotensin II from angiotensin I), blockers/antagonists of angiotensin II receptor type 1 (AT,R) such as losartan and its derivatives, and recombinant ACE2, which is considered as a decoy for recognition and competitive binding to the spike glycoprotein of SARS-CoV-2 [3, 4].

Importantly, Kidde and Sahebkar mentioned in their recent article the potential interest of nitric oxide and the ACE2-angiotensin(1–7)-Mas axis in COVID-19 [1]. We wish to underline here that the nitric oxide is basically too reactive (with a very short half-life of 5 sec) to constitute an appropriate therapeutic target [5], and also that this counter-regulatory RAS pathway is actually wider and involves not only the Mas receptor targeted by angiotensin 1-7, but also the vasodilator receptors ACE2 receptor targeted by angiotensin A, AT,R targeted by angiotensin 1-9, MrgD targeted by alamandine, and AT,R targeted by angiotensin IV (Fig. 1) [6]. All these natural molecules display several key and unique advantages. First, the molecules are peptides, which are non-toxic compounds as compared to organic molecules (e.g., ACE inhibitors and AT,R antagonists/blockers) because they degrade into safe amino acids and related metabolites. In addition, the negative regulation driven by the counter-regulatory RAS peptides occurs naturally in humans to counteract the over-stimulated RAS (unlike ACE inhibitors and AT,R antagonists/blockers). Finally, the receptors targeted in the counter-regulatory RAS are different from the ACE and AT,R receptors and are naturally stimulated in humans to counteract the over-stimulation of RAS, indicating that the use of their natural ligands is the most relevant and appropriate chemotherapeutic strategy in COVID-19.

Based on these considerations, and rather than nitric oxide, we support the use of these natural peptide drug candidates belonging to the counter-regulatory RAS, namely angiotensin 1-7, angiotensin A, angiotensin 1-9, alamandine and/or angiotensin IV, to neutralize the SARS-CoV-2-induced RAS overreaction and to prevent and treat COVID-19 outcomes.

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Fig. (1). Renin-angiotensin system (RAS) and counter-regulatory RAS pathways, with inhibiting effects of SARS-CoV-2 on ACE2. ACE: Angiotensin-Converting Enzyme; ACE2: Angiotensin-Converting Enzyme 2; AD: aspartate decarboxylase; APA: aminopeptidase A; APN: aminopeptidase N; AT1R: angiotensin II receptor type 1; AT2R: angiotensin II receptor type 2; AT3R: angiotensin II receptor type 3; AT4R: angiotensin II receptor type 4; MasR: Mas receptor; MRGD: Mas-related G protein-coupled receptor member D.

AUTHORS’ CONTRIBUTIONS

- CA has full access to all of the data in the study, takes responsibility for the data, the analyses, and interpretation, and has the right to publish any and all data, separate and apart from the attitudes of the sponsors. All authors have read and approved the manuscript.
- CA, ZC, NP, HK, JMS were responsible for study concept and design.
- Acquisition of data: Not applicable.
- CA, ZC, NP, HK, JMS were responsible for analysis and interpretation of data.
- CA and JMS were responsible for drafting of the manuscript.
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