Understanding the renin–angiotensin–aldosterone–SARS-CoV axis: a comprehensive review

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The interplay of SARS-CoV-2 with the renin–angiotensin–aldosterone system probably accounts for much of its unique pathology. Appreciating the degree and mechanism of this interaction highlights potential therapeutic options, including blockade (ARBs). https://bit.ly/3aue4tS


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ABSTRACT

Importance: Coronavirus disease 2019 (COVID-19), the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been declared a global pandemic with significant morbidity and mortality since first appearing in Wuhan, China, in late 2019. As many countries are grappling with the onset of their epidemics, pharmacotherapeutics remain lacking. The window of opportunity to mitigate downstream morbidity and mortality is narrow but remains open. The renin–angiotensin–aldosterone system (RAAS) is crucial to the homeostasis of both the cardiovascular and respiratory systems. Importantly, SARS-CoV-2 utilises and interrupts this pathway directly, which could be described as the renin–angiotensin–aldosterone–SARS-CoV (RAAS–SCoV) axis. There exists significant controversy and confusion surrounding how anti-hypertensive agents might function along this pathway. This review explores the current state of knowledge regarding the RAAS–SCoV axis (informed by prior studies of SARS-CoV), how this relates to our currently evolving pandemic, and how these insights might guide our next steps in an evidence-based manner.

Observations: This review discusses the role of the RAAS–SCoV axis in acute lung injury and the effects, risks and benefits of pharmacological modification of this axis. There may be an opportunity to leverage the different aspects of RAAS inhibitors to mitigate indirect viral-induced lung injury. Concerns have been raised that such modulation might exacerbate the disease. While relevant preclinical, experimental models to date favour a protective effect of RAAS–SCoV axis inhibition on both lung injury and survival, clinical data related to the role of RAAS modulation in the setting of SARS-CoV-2 remain limited.

Conclusion: Proposed interventions for SARS-CoV-2 predominantly focus on viral microbiology and aim
to inhibit viral cellular injury. While these therapies are promising, immediate use may not be feasible, and the time window of their efficacy remains a major unanswered question. An alternative approach is the modulation of the specific downstream pathophysiological effects caused by the virus that lead to morbidity and mortality. We propose a preponderance of evidence that supports clinical equipoise regarding the efficacy of RAAS-based interventions, and the imminent need for a multisite randomised controlled clinical trial to evaluate the inhibition of the RAAS–SCoV axis on acute lung injury in COVID-19.