jraas

Journal of the Renin-Angiotensin-Aldosterone System
October-December 2020: 1–5

DOI: 10.1177/1470320320972018
journals.sagepub.com/home/jra
SAGE

Countermeasure and therapeutic: A(1–7) to treat acute respiratory distress syndrome due to COVID-19 infection

Maira Soto[1], Gere diZerega[2] and Kathleen E Rodgers[1]

Abstract

In the wake of the COVID-19 pandemic it has become clear that there is a need for therapies that are capable of reducing damage caused to patients from infections. Infections that induce Acute Respiratory Distress Syndrome (ARDS) are especially devastating because lung damage is so critical and difficult to manage. Angiotensin (1–7) [A(1–7)] has already been shown to protect pulmonary health and architecture in various models of disease. There is also evidence that A(1–7) can modulate immune function and protect various organs (lung, kidney, and heart) from oxidative damage and inflammation. Here we focus on making a case for the development of novel therapies that target the protective arm of the Renin Angiotensin System (RAS).

Keywords

COVID, ARDS, respiratory infection, angiotensin (1–7), ACE2

Date received: 27 April 2020; accepted: 16 October 2020

Introduction

The late-stages of SARS-CoV-2 (the virus responsible for the COVID-19 pandemic) infection are characterized by acute respiratory distress syndrome (ARDS), wide-spread inflammation, and damage to the heart, the liver, and the kidneys, that ultimately results in multiple organ failure and death.[1] The sudden influx of patients into intensive care units has overwhelmed healthcare systems globally. With the number of COVID-19 cases in the United States exceeding all other countries (as of November 2, 2020) and increasing SARS-CoV-2, presents an acute and urgent threat to global health security. Therapeutic interventions capable of reducing symptomatic severity would reduce the fatality rate, improve long term outcomes, and free up scarce Intensive Care Unit (ICU) resources.

SARS-CoV-2 binds to the cell surface protein receptor,[2] ACE2, a member of the ACE2/A(1–7)/Mas axis. COVID-19 pathology emerges, in part, due to the reduced ability of ACE2 to cleave angiotensin II (A-II), a pro-inflammatory, fibrotic peptide, to angiotensin 1–7 (A(1–7)). A(1–7) is the endogenous ligand of the Mas receptor and a member of the ACE2/A(1–7)/Mas axis. A(1–7) counteracts the effects of A-II and mobilizes endogenous regenerative processes.[3]

Late-stages of SARS-CoV-2 infection are characterized by ARDS, wide-spread inflammation, and damage to the heart, liver, and kidneys, as well as death. Critically, A(1–7) has been shown in pre-clinical and clinical studies to protect the organ systems affected by SARS-CoV-2. The scientific, pre-clinical and clinical data strongly suggest A(1–7) to be a safe and efficacious IV drug able to (a) disrupt an arm of COVID-19-induced pulmonary pathology and (b) act as a regenerative therapeutic.

ARDS presents as a syndrome of acute respiratory failure defined by bilateral lung infiltrates and physiological criteria in which widespread damage to cells and structures of the lung occurs within hours to days.[1] ARDS occurs as a consequence of critical illness of diverse etiologies, including

[1]Department of Pharmacology, College of Medicine, Center for Innovation in Brain Science, University of Arizona, Tucson, AZ, USA
[2]USBiotest, San Luis Obispo, CA, USA

Corresponding author:
Kathleen E Rodgers, Department of Pharmacology, College of Medicine, Center for Innovation in Brain Science, University of Arizona, 1230 N Cherry Ave, Tucson, AZ 85721-0202, USA.
Email: krodgers@email.arizona.edu

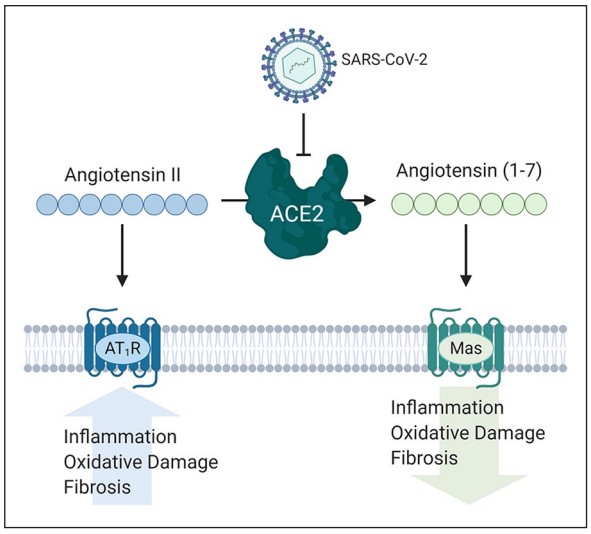

Figure 1. SARS-CoV-2 binds to ACE2 resulting in increased levels of Ang-II. Administration of A(1–7) will restore the balance of the two RAS axis.

SARS-CoV-2 infection. The pathologic hallmarks of human ALI/ARDS from any cause includes neutrophilic alveolitis, hyaline membranes secondary to protein transudation and precipitation in the airspace, microthrombi secondary to the generation of procoagulant mediators and endothelial injury, and epithelial and endothelial injury.

Mechanistic overview of COVID-19 and the Renin Angiotensin System

The Renin-Angiotensin System (RAS) can be thought of as a hormonal system with two axes—the ACE/Ang-II/AT_1R axis (pathological arm) and the counter-regulatory ACE2/A(1–7)/Mas receptor axis (protective arm). The ACE/Ang-II/T_1R axis has now been implicated in pulmonary, cardiovascular, renal and central nervous system pathophysiology.[3] In vivo, Mas acts as a functional antagonist of the AT_1R, thereby inhibiting the actions of A-II.[4] A(1–7) is the endogenous ligand of the Mas receptor and a member of the protective RAS.

SARS-CoV-2, like SARS, binds to the cell surface protein receptor, ACE2, a member of the ACE2/A(1–7)/Mas axis. SARS pathology emerges, in part, due to the reduced ability of ACE2 to cleave Ang-II, a pro-inflammatory, fibrotic peptide, to A(1–7) (Figure 1).[2] Ang-II is a potent vasoconstrictor that can increase lung injury and lung edema.[5] A(1–7) counteracts the effects of angiotensin II and mobilizes endogenous regenerative processes.[4] In SARS-infected animals, increased levels of Ang-II were observed due to reduced ACE2 activity. In this study ACE2 cleaves angiotensin II to A(1–7), thereby reducing the pathological activities of angiotensin II and increasing the protective arm of the RAS through the ACE2/A(1–7)/Mas axis.[6] These data suggest the hypothesis that IV treatment with A(1–7) would reduce inflammation and oxidative stress, as well as rebalance the RAS. Moreover, the use of A(1–7) to combat SARS-CoV-2 is finding support in the peer-reviewed literature.[7]

Clinical observations supporting a role for A(1–7)

In a recent study of ICU patients with ARDS, increased serum levels of A(1–10) and reduced serum levels of A(1–7) at the time of admission, which indicates dysregulation of angiotensin peptide metabolism, were observed in those patients that did not survive.[8] Importantly, patients with this degree of dysregulation of angiotensin peptide metabolism did not survive, despite aggressive ventilator-assisted pulmonary therapy. Further, a recent publication showed that circulating Ang-II levels increased with increased SARS-CoV-2 viral load and reduced Pa02/Fi02 levels.[9]

Mechanistic studies supporting a role for A(1–7) in the treatment of ARDS

Our proposed treatment of humans with COVID-19 induced ARDS by A(1–7) is also supported by animal models of ARDS (ventilator, oleic acid, and sepsis induced), pulmonary hypertension (PH), and fibrosis.[10–17] Consistent across these studies is an imbalance between ACE/Ang II/AT1 and the ACE2/Ang-(1–7)/Mas axis of the RAS occurring in animals with lung disease.

In an experimental study published in Nature in 2005, Imai et al.[6] showed that ACE2, which converts A-II to A(1–7) by cleavage of one amino acid, protects mice from ARDS induced by acid aspiration or sepsis. This is attributed to the fact that ACE2 will decrease A-II concentration and thus, reduce the activation of the AT_1R. A separate study by Shenoy et al.[14] in rats showed positive effects in a pulmonary fibrosis model using lentiviral packaged A(1-7)-fusion genes or ACE2 cDNA. Overexpression of A(1–7) significantly prevented the associated negative effects of pulmonary fibrosis, namely: (1) increase in right ventricular systolic pressure and development of right ventricular hypertrophy; (2) excessive collagen deposition; (3) the decreased expression of ACE and ACE2; (4) increased pro-inflammatory cytokines; and (5) increased protein levels of the AT_1R. Overexpression of ACE2 achieved similar protective effects. Blockade of the Mas receptor abolished the beneficial effects of A(1–7), confirming the role of the Mas receptor and A(1–7) in protection of the lung.

In vivo, A(1–7) protects against ventilator-induced ARDS in mice.[15] Male C57/Bl6J mice were randomly assigned to three groups of five animals each. Animals in Group 1 (low V_t) were continuously ventilated with a tidal volume (V_t) of 10 mL/kg and a positive end-expiratory pressure of 2 mmHg.

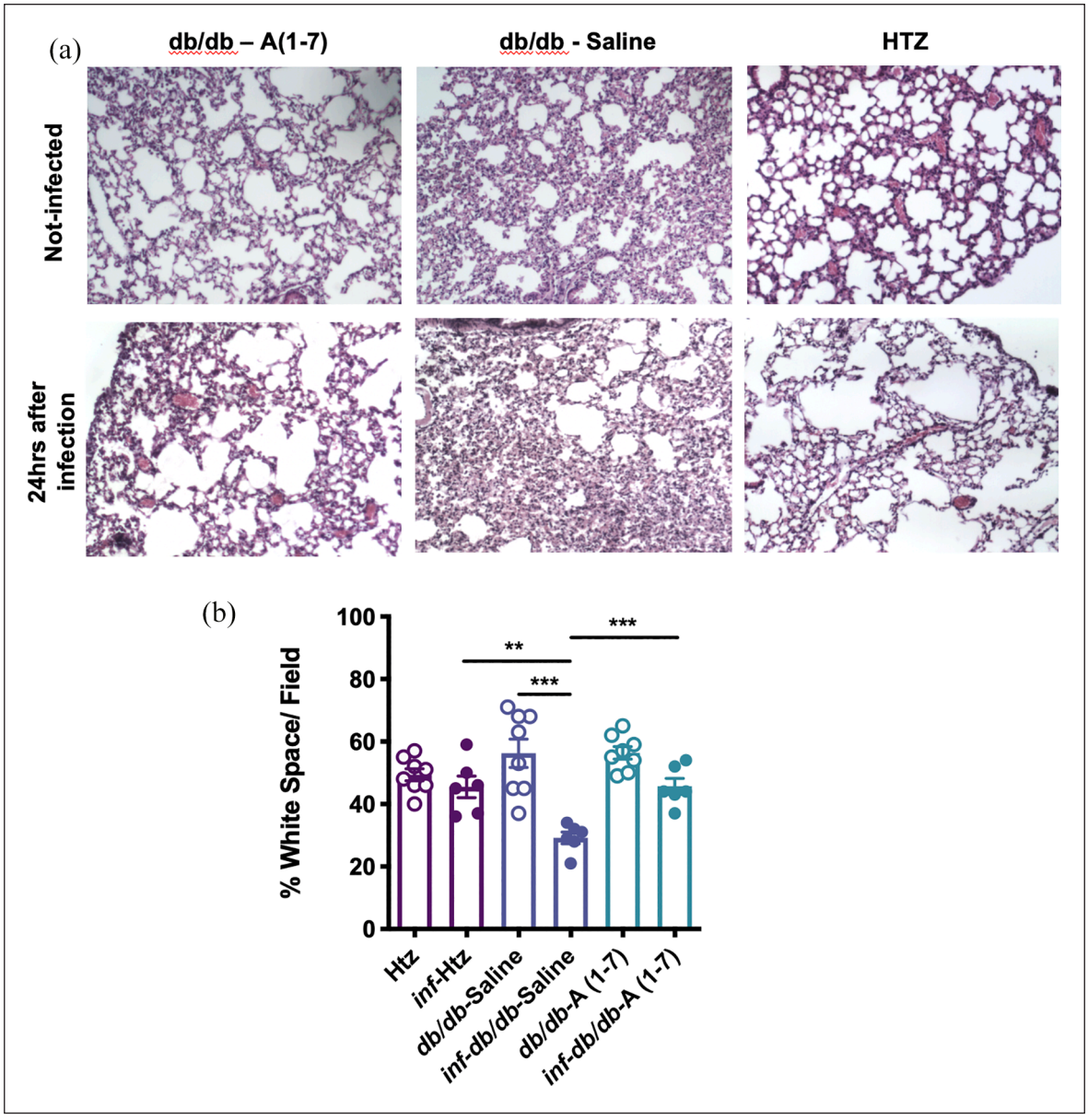

Figure 2. Clearance of pulmonary infection in diabetic mice treated with A(1–7). Diabetic (db/db) mice have difficulty breathing and show impaired clearance of lung infections versus controls (htz). There is no difference in alveolar volume between db/db mice and htz with no pulmonary infections (a and b). 24 h after intra-tracheal bowls of S. aureus (c), saline treated db/db mice continued to show significant PMN cell versus htz or A(1–7) treated mice. Statistics were run using Prism 8.4.0, *t*-tests were used to compare all groups to saline treated db/db mice; $^{**}p < 0.01$, $^{***}p \leq 0.001$.

In Group 2 (high V_t), ventilator-induced severe hypoxemia and pulmonary edema (ARDS) was induced by over-ventilation with tidal volumes of 20 mL/kg and a positive end-expiratory pressure of 2 mmHg. In Group 3 (high V_t +A(1–7)), VILI was induced as in Group 2, and infusion of Angiotensin 1–7 at 5 pmol/kg per minute was initiated with the start of high tidal volume ventilation. Over-ventilation with high tidal volumes of 20 mL/kg caused ventilator-induced ARDS, evident as increased lung wet-to-dry weight ratio, decreased arterial oxygenation, and increased lung myeloperoxidase (MPO) activity. A(1–7) largely attenuated the development of ARDS, as demonstrated by a normalization of the lung wet-to-dry weight ratio and MPO activity, and a significant improvement in arterial oxygen partial pressure (PaO_2).

A(1–7) also protects against oleic acid (OA)-induced ALI/ARDS in Sprague-Dawley rats.[16] In this study, animals in Group 1 (control) did not receive any pharmacological interventions. In Group 2, ALI was induced by intravenous infusion of 0.2 mg/kg OA in the absence of any treatment. In Group 3 (OA+A(1–7)), ALI was induced as in Group 2, and infusion of A(1–7) at 5 pmol/kg per minute was

initiated 30 min after ALI induction. A(1–7) attenuated the development of OA-induced ARDS, as demonstrated by the fact that A(1–7) infusion abrogated OA-induced changes in lung wet-to-dry weight ratio and MPO activity, and significantly reduced increases in BAL protein concentration and pulmonary vascular resistance (PVR).

In a more recent study, A(1–7) was able to improve pulmonary function, including prolonged improvement in oxygenation, reduction in inflammatory cells recruitment and reduction in lung fibrosis long term in an animal model of ARDS involving two insults, acid instillation and prolonged injurious ventilation. Notably, Ang-(1–7) was effective even after delayed administration.[17]

Benefits of A(1–7) in diabetes, pneumonia and systemic organ failure

Diabetic patients are at higher risk for infection and severe complications from SARS-CoV-2 infection.[18] Increased oxidative stress and chronic inflammation has deleterious effects on kidney, heart and lung health in these patients; this is only more exacerbated with SARS-CoV-2 infection.[19,20] Long and short-term administration of A(1–7) treatment in diabetic mice has improved lung, heart and kidney function by reducing oxidative stress and inflammation.[21–24] In diabetic mice, Resident alveolar macrophages are depleted in diabetic mice and restored to normal levels with A(1–7) treatment.[24] Further, data from SARS patients suggests that disease severity is correlated with an immune dysregulation in neutrophil clearance commonly seen in diabetic patients. Again, A(1–7) has been shown to restore proper pathogen clearance and immune resolution of neutrophils. Results from an unpublished study using a bacterial model of pneumonia, show that treatment with A(1–7) reduced lung congestion 24 h after infection (Figure 2).

Finally, in an unpublished study of bone marrow transplant following lethal irradiation, mice began to die due to an unplanned norovirus infection at day 3 after transplant. In mice that received donor cells from the saline treated animals and saline treatment after transplant, there was only 20% survival (Figure 3). In A(1–7) treated mice (both donor and recipient), there was 100% survival. These data show that A(1–7) not only ameliorates sequelae secondary to infection, but also prevents multiple organ system failure and death.

Conclusion

There is an immediate need for treatments to help patients fighting this COVID-19 pandemic. Beyond this pandemic, there is need for therapeutics for future pandemics that are not pathogen specific and act by supporting natural healing processes. A(1–7) can act by several mechanisms to improve overall outcomes in respiratory infections; specifically anti-fibrotic properties and immune resolution that are very important in lung health. Further, A(1–7) has also shown to be effective in ameliorating systemic organ damage caused by oxidative stress and inflammation, both important contributors of death in severe infections like this COVID-19 pandemic.

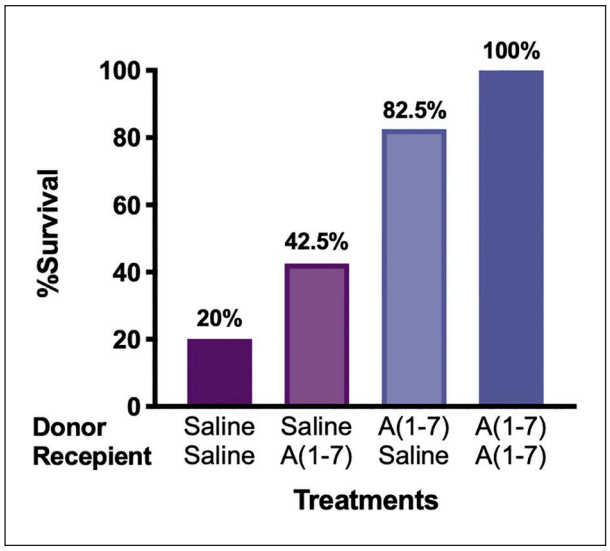

Figure 3. A(1–7) treatment has the potential to improve outcomes after viral infection of immunocompromised mice. C57BL/6 mice ($n = 40$/group) were transplanted after total body irradiation myeloablation. Saline or A(1–7) treated donors (above) and received saline or A(1–7) after transplant. Treatment of either donors or recipients with A(1–7) improved recipient survival upon exposure to pathogenic virus (unpublished data).

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Kathleen E Rodgers https://orcid.org/0000-0002-7994-8894

References

1. Fahy RJ, Lichtenberger F, McKeegan CB, et al. The acute respiratory distress syndrome. *Am J Respir Cell Mol Biol* 2012; 28: 499–503.
2. Zhou P, Yang X, Wang X, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; 579(7798): 270–273.
3. Ruan X, Varghese Z and Moorhead J. An update on the lipid nephrotoxicity hypothesis. *Nat Rev Nephrol* 2009; 5(12): 713–721.

4. Kostenis E, Milligan G, Christopoulos A, et al. G-Protein–coupled receptor mas is a physiological antagonist of the angiotensin II type 1 receptor. *Circulation* 2005; 111(14): 1806–1813.
5. Flemming A. Unravelling SARS lethality. *Nat Rev Drug Discovery* 2005; 4(9): 718–718.
6. Imai Y, Kuba K and Penninger JM. The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice. *Exp Physiol* 2008; 93(5): 543–548.
7. Peiró C and Moncada S. Substituting Angiotensin-(1-7) to prevent lung damage in SARSCoV2 Infection? *Circulation* 2020; 141(21): 1665–1666.
8. Reddy R, Asante I, Liu S, et al. Circulating angiotensin peptides levels in acute respiratory distress syndrome correlate with clinical outcomes: a pilot study. *PLoS One* 2019; 14(3): e0213096.
9. Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci* 2020; 63(3): 364–374.
10. Fleming I, Kohlstedt K and Busse R. New fACEs to the renin-angiotensin system. *Physiology* 2005; 20(2): 91–95.
11. Ishiyama Y, Gallagher P, Averill D, et al. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. *Hypertens J Am Hear Assoc* 2004; 43(5): 970–976.
12. Donoghue M. Heart block, ventricular tachycardia, and sudden death in ACE2 transgenic mice with downregulated connexins. *J Mol Cell Cardiol* 2003; 35(9): 1043–1053.
13. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 2005; 436(7047): 112–116.
14. Shenoy V, Ferreira AJ, Qi Y, et al. The angiotensin-converting enzyme 2/angiogenesis-(1-7)/Mas axis confers cardiopulmonary protection against lung fibrosis and pulmonary hypertension. *Am J Respir Crit Care Med* 2010; 182(8): 1065–1072.
15. Walther T, Kuebler W and Berlin CU. *Use of an ang-(1-7) receptor agonist in acute lung injury*. Patent application 13/063,685, USA, 2011
16. Yamazato Y, Ferreira AJ, Hong K-H, et al. Prevention of pulmonary hypertension by angiotensin-converting enzyme 2 gene transfer. *Hypertension* 2009; 54(2): 365–371.
17. Zambelli V, Bellani G, Borsa R, et al. Angiotensin-(1-7) improves oxygenation, while reducing cellular infiltrate and fibrosis in experimental acute respiratory distress syndrome. *Intensive Care Med Exp* 2015; 3(1): 1–17.
18. Zhou J and Tan J. Diabetes patients with COVID-19 need better care. *Metab Clin Exp* 2020;107: 154216.
19. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol Off J Ger Cardiac Soc* 2020; 109(5); 1–8.
20. Hussain A, Moreira NC do V, Home P, et al. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. *Diabetes Metab Syndrome Clin Res Rev*. Epub ahead of print 2020. DOI: 10.1016/j.dsx.2020.04.002.
21. Papinska AM, Soto M, Meeks CJ, et al. Long-term administration of angiotensin (1-7) prevents heart and lung dysfunction in a mouse model of type 2 diabetes (db/db) by reducing oxidative stress, inflammation and pathological remodeling. *Pharmacol Res* 2016; 107: 372–380.
22. Papinska AM, Mordwinkin NM, Meeks CJ, et al. Angiotensin-(1-7) administration benefits cardiac, renal and progenitor cell function in db/dbmice. *Br J Pharmacol* 2015; 172(18): 4443–4453.
23. Papinska AM and Rodgers KE. Long-term administration of angiotensin (1-7) to db/db Mice reduces oxidative stress damage in the kidneys and prevents renal dysfunction. *Oxid Med Cell Longev* 2018; 2018: 1841046.
24. Soto M, Gaffney KJ and Rodgers KE. Improving the innate immune response in diabetes by modifying the renin angiotensin system. *Front Immunol* 2019; 10: 2885.