Obesity

Angiotensin-(1-7) and Obesity: Role in Cardiorespiratory Fitness and COVID-19 Implications

Daisy Motta-Santos [1,2], *Robson A. S. Santos*[2], *and Sérgio Henrique Sousa Santos* [3,4]

TO THE EDITOR: We have read with interest the recent review by Zbinden-Foncea et al. (1) suggesting that high levels of cardiorespiratory fitness induced by prior exercise training may confer some innate immune protection against coronavirus disease (COVID-19) by attenuating the "cytokine storm syndrome" by modulating angiotensin-converting enzyme 2 (ACE2) effects. However, it is important to highlight that the benefic effects of physical exercise also involves the angiotensin-(1-7)/MAS1 proto-oncogene, GPCR receptor (MAS receptor; Mas) axis activation.

Ang-(1-7) anti-inflammatory actions have been described for more than 10 years (2), being produced by human vascular endothelium (3). Arterial hypertension, asthma, diabetes, and obesity are some of the chronic diseases associated with Ang-(1-7)/Mas axis unbalance (2,4). These persistent conditions are all improved by Ang-(1-7) or its homologues treatments. The beneficial mechanisms are correlated with improved inflammation resolution, protection against endotoxin-induced muscle wasting (5), Toll-like receptor 4 activation, and nuclear factor-KB pathway modulation (6). Physical training also promotes similar anti-inflammatory effects, which could be complementary or additive.

Recent studies have suggested that physical training is able to modulate the renin-angiotensin system, including the ACE2 expression and activity. Some important data have shown that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binding with ACE2 promotes its internalization (7), which partially prevents Ang-(1-7) formation from ACE2. The Ang-(1-7) downproduction could be associated with COVID-19 complications. Some clinical studies have shown that the ACE inhibitor (iACE) and AT1 blocker (BRA) use could be beneficial in the clinical outcomes of hypertensive patients or those with SARS-CoV-2 infection (7). It is important to note that these antihypertensive agents act by direct modulation of the renin-angiotensin system, as well as are observed in response to physical training.

Recent publications have suggested use of Ang-(1-7) in treating COVID-19 complications and associated diseases (8), and three clinical trials have recommended the Ang-(1-7) level normalization for SARS-CoV-2–infected patients (https://clinicaltrials.gov/ct2/show/NCT04332666, https://www.clinicaltrials.gov/ct2/show/NCT04401423, and https://clinicaltrials.gov/ct2/show/NCT04375124).

Genetic deletion of ACE2 in mice decreases physical performance (9), and the Mas receptor mediates cardiac and metabolic adaptations induced by physical training (10). Therefore, it is important to highlight that the possible protective effects of physical training may involve the mainstream actions of the ACE2/Ang-(1-7)/Mas axis.

The lack of Ang-(1-7) receptor (Mas) is also associated with several changes in the immune and metabolic system, demonstrating its importance and participation in anti-inflammatory protection and resolution of inflammation (2,4). Recently, a study demonstrated that people with obesity and preterm adolescents with arterial hypertension have reduced levels of Ang-(1-7) (11).

Metabolic syndrome, aging, obesity, diabetes, hypertension, and some other cardiometabolic chronic diseases have been described as risk factors for severe complications and mortality in patients with COVID-19. All these persistent disorders have also been described to be improved by increased Ang-(1-7) levels (2,7,8).

The SARS-CoV-2 symptoms and the consequent prognosis could be worsened in individuals with obesity/overweight, insulin resistance/diabetes, and sedentary lifestyle. Clinical outcomes in these patients are linked to deregulated lipid synthesis and increased cytokines released by the adipose tissue (8) associated with the inflammatory state (2).

Funding agencies: The present study was partially supported by grants from FAPEMIG, CAPES, and CNPq.

Disclosure: The authors declared no conflict of interest.

References

1. Zbinden-Foncea H, Francaux M, Deldicque L, Hawley JA. Does high cardiorespiratory fitness confer some protection against pro-inflammatory responses after infection by SARS-CoV-2? *Obesity (Silver Spring)* 2020;28:1378-1381.
2. Lelis DF, Freitas DF, Machado AS, Crespo TS, Santos SHS. Angiotensin-(1-7), adipokines and inflammation. *Metabolism* 2019;95:36-45.
3. Schinzari F, Tesauro M, Veneziani A, Mores N, Di Daniele N, Cardillo C. Favorable vascular actions of angiotensin-(1-7) in human obesity. *Hypertension* 2018;71:185-191.
4. Santos RAS, Sampaio WO, Alzamora AC, et al. The ACE2/angiotensin-(1–7)/MAS axis of the renin-angiotensin system: focus on angiotensin-(1-7). *Physiol Rev* 2018;98:505-553.
5. Morales MG, Olguin H, Di Capua G, Brandan E, Simon F, Cabello-Verrugio C. Endotoxin-induced skeletal muscle wasting is prevented by angiotensin (1-7) through a p38 MAPK dependent mechanism. *Clin Sci (Lond)* 2015;129:461-476.
6. Santos SH, Andrade JM, Fernandes LR, et al. Oral angiotensin-(1-7) prevented obesity and hepatic inflammation by inhibition of resistin/TLR4/MAPK/NF-kappaB in rats fed with high-fat diet. *Peptides* 2013;46:47-52.
7. Peiró C, Moncada S. Substituting angiotensin-(1–7) to prevent lung damage in SARS-CoV-2 infection? *Circulation* 2020;141:1665-1666.
8. Magalhães GS, da Rodrigues-Machado MG, Motta-Santos D, et al. Activation of Ang-(1–7)/Mas receptor is a possible strategy to treat coronavirus (SARS-CoV-2) infection. *Front Physiol* 2020;11:730. doi:10.3389/fphys.2020.00730
9. Motta-Santos D, Dos Santos RA, Oliveira M, et al. Effects of ACE2 deficiency on physical performance and physiological adaptations of cardiac and skeletal muscle to exercise. *Hypertens Res* 2016;39:506-512.
10. Filho AG, Ferreira AJ, Santos SH, et al. Selective increase of angiotensin(1–7) and its receptor in hearts of spontaneously hypertensive rats subjected to physical training. *Exp Physiol* 2008;93:589-598.
11. South AM, Nixon PA, Chappell MC, et al. Obesity is associated with higher blood pressure and higher levels of angiotensin II but lower angiotensin-(1–7) in adolescents Born Preterm. *J Pediatr* 2018;205:55-60.e1.

[1] Sports Department, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil [2] INCT NanoBiofar, Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil [3] Postgraduate Program in Health Science, Universidade Estadual de Montes Claros (Unimontes), Montes Claros, Minas Gerais, Brazil. Correspondence: Sérgio Henrique Sousa Santos (sergiosousas@hotmail.com) [4] Institute of Agricultural Sciences (ICA), Food Engineering, Universidade Federal de Minas Gerais, Montes Claros, Minas Gerais, Brazil.

doi: 10.1002/oby.22949