Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

European Journal of Pharmacology 883 (2020) 173373

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Full length article

Correlation between renin-angiotensin system and Severe Acute Respiratory Syndrome Coronavirus 2 infection: What do we know?

Antonio Vitiello, Francesco Ferrara *

Usl Umbria 1, Perugia, Italy

ARTICLE INFO

Keywords:
ACE-2
Coronavirus
Infection
RAS
SARS-CoV-2
Pharmacology
Renin

ABSTRACT

The first cases of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2 or COVID-19) infections were recorded in China in November 2019. Since its appearance in China at the end of last year, the virus has spread to all continents causing a "global pandemic".

To date, some aspects remain to be investigate about the pathophysiology of this viral infection. One of the aspects to be still clarified is the correlation between the renin-angiotensin system (RAS) and SARS-CoV-2 infection. RAS is a physiological system playing a key role in different human body functions regulation. SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE-2), a component of RAS, as a potential factor of cell penetration and infectivity; in addition, in the different infection stages, a functional variation of the RAS has been noted. In this article, we discuss the correlation between the role of RAS and system-modifying agents, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) and direct renin inhibitors (DRIs), with SARS-CoV-2 infection.

1. Introduction

A new Coronavirus SARS-CoV-2 (COVID-19) has been identified as the cause of Severe Acute Respiratory Syndrome (SARS), a severe form of viral pneumonia associated with high mortality. This virus spread from China to the rest of the world into a real short period and with an important severity, leading the World Health Organization (WHO) to consider a "global emergency".

SARS-CoV-2 is a RNA virus sharing about 80% of the viral genome with SARS-CoV (responsible for the 2003 outbreak) (Wu, 2020).

Several studies confirmed that the virus is able to penetrate into human cells by binding to ACE-2 protein, the angiotensin-converting enzyme 2, which is part of the renin-angiotensin system (RAS) (Guoping et al., 2020) and considered as a possible membrane receptor. It has also been noted that patients infected by this virus, during the sick days, have functional variations in the concentrations of enzymes components of the RAS (Huang et al., 2020; Zhou et al., 2020). This is a defense mechanism of the human host that helps against the infection or is responsible for a worsening of clinic?al conditions and, as consequence, to be corrected pharmacologically? (Gurwitz, 2020)

2. The correlation between RAS and SARS-CoV-2

The renin-angiotensin system (RAS) is a physiological mechanism able to regulate different functions of the body, in particular the most important are the regulation of blood pressure, the volume of circulating plasma (volemia) and the tone of the arterial muscles through different mechanisms. RAS is an enzymatic cascade; the main enzyme pathway (classical) is renin which converts the angiotensinogen, released by the liver, into angiotensin I (Ang I). Ang I is subsequently converted to angiotensin II (Ang II) by the angiotensin-converting enzyme (ACE). There is also another (non-classical) enzyme pathway, mediated by ACE-2 (Atlas, 2007), in this pathway ACE-2 converts Ang II to angiotensin 1-7 (Ang 1–7) and Ang I to angiotensin 1-9 (Ang 1–9).

ACE-2 is a type I membrane metallocarboxypeptidase with high ACE homology, the functions are distinct and the two enzymes are also expressed differently in tissues. For example, ACE-2 is most expressed in renal, cardiovascular, pulmonary and gastrointestinal tissues, ACE activity is highly expressed in the lungs, brain and kidneys (Nehme et al., 2019). Some aspects on the correlation between the various stages of SARS-CoV-2 infection and the RAS variation remain to be clarified. SARS-CoV-2 infection has been divided into three phases: the first asymptomatic or slightly symptomatic, the second and the third more

* Corresponding author.
E-mail address: francesco.ferrara@uslumbria1.it (F. Ferrara).

https://doi.org/10.1016/j.ejphar.2020.173373
Received 12 May 2020; Received in revised form 10 July 2020; Accepted 13 July 2020
Available online 15 July 2020

severe, characterized by hyperinflammatory state. In the second and third phase it seems that the worst damage is caused by a generalized inflammatory state, caused by a "cytokine storm" and responsible for severe lung injury and multi-organ dysfunction (Watkins, 2020).

Several studies have shown that variation in the RAS can be very related to SARS-CoV-2 infection, and involved in all stages.

ACE-2 has been identified as an input membrane receptor for SARS-CoV-2 in epithelial lung cells; this evidence may suggest that increased expression of ACE-2 is related to an increased risk of SARS-CoV-2 infection.

In addition, as described above, variations in RAS were noted during the various stages of SARS-CoV-2 infection; in particular, the evidence showed increased activation of the system in the early stages, and then decreased in subsequent stages, although the data showing these variations are conflicting and not entirely clear (Zheng et al., 2020; Fang et al., 2020). Certainly, the activation of RAS is known to change in conditions such as COPD, asthma, during viral infections and in smokers, demonstrating that the system is related to correct lung and airway function. The evidence suggests that the physiological balance of the RAS system and especially between ACE/ACE-2 is likely to be altered by SARS-CoV-2 viral infection. This RAS imbalance is likely to play a role in lung lesion and inflammatory state activation, but these aspects have yet to be clarified. In this direction, the pharmacological approach to regulated the concentration of ACE/ACE-2 could be a way to moderate severe lung damage virus-induced (Bavishi et al., 2016; Ferrario et al., 2005). In addition, ACE-2 has been shown to play a role in fibrogenesis and inflammation of different organs, including the lungs. Studies in patients infected with SARS-CoV-2 showed that ACE-2 expression has a rapid increase in the first hours of viral infection, then begins rapid down-regulation in the lung tissue when the patient enters stage two and three of the infection. However, it can be possible that ACE-2 has a protective effect and when it decreases there is a worsening of the lungs inflammatory state. In addition, specific studies show that ACE-2 expression is decreased in respiratory diseases, such as pulmonary fibrosis or COPD. It should also be noted that Ang II, Ang 1–7 and Ang 1–9 have different biological effects. In fact, the biological effects of Ang II are vasoconstrictor and aldosterone release stimulant; but can cause also myocardial hypertrophy, interstitial fibrosis, endothelial dysfunction, increase of inflammation state, oxidative stress and increased of coagulation, biological effects that, if altered, can cause serious complications in a patient with SARS-CoV-2 infection (Zhang et al., 2020). Ang II can cause increased inflammation through production of IL-6, TNF (Tumor Necrosis Factor) and other inflammatory cytokines (Recinos et al., 2006; Yamamoto et al., 2011; Lee et al., 2002).

However, it is important to note that all these biological effects are mediated by AT-1 receptors (AT-1r). ACE-2 can reduce the negative effects of Ang II through several mechanisms, for example by the conversion of Ang II to Ang 1–7. Ang1-7 has opposite biological effects to Ang II through the Mas receptor (MASr) and Type II receptors of Ang II (AT-2r). The MASr are expressed on the surface of bronchial muscle and alveolar epithelium of the lungs (Magalhaes et al., 2015), and the Ang 1–7 has anti-inflammatory and antifibrosis effects by MASr agonist effect (Chen et al., 2013; Meng et al., 2014).

In addition, MASr are expressed on platelets, and Ang 1–7 mediates the antiaggregant effects (Fang et al., 2013; Pai et al., 2017; Fraga-Silva et al., 2011) because it is able to increase prostacyclines (Fraga-Silva et al., 2008). This description suggest that pharmacological modulation of RAS at different stages of SARS-CoV-2 infection could be a beneficial and effective therapy.

3. The pharmacological approach by modulating RAS in SARS-CoV-2 infection

A pharmacological approach modulating RAS could be of clinical benefit to fight SARS-CoV-2 infection. Agents acting on RAS can be distinguished as angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) and direct renin inhibitors (DRIs) (Bavishi et al., 2020).

These agents are currently indicated for the treatment of various cardiovascular diseases with excellent clinical efficacy. ACEIs are able to reduce blood pressure by acting with ACE inhibition which converts Ang I to Ang II. ARBs are Ang II antagonists on the type 1 receptor (AT-1r), finally, DRIs block plasma renin activity and inhibit the conversion of angiotensinogen to Ang I. The three different classes described above have different effects on the regulation and enzymatic expression of RAS. In fact, on the basis of *in vitro* studies, it seems that the use of ACEIs, with a blockade of the enzyme ACE, increases the expression of the enzyme ACE-2 (stimulating other synthesis pathways), although these data are not fully confirmed and at the moment very contradictory (Vaduganathan et al., 2020). The use of ARBs seems to be linked to a slight increase in the expression of both ACE and ACE-2. Finally, the use of DRIs, by inhibiting the upstream RAS cascade, seems to inhibit expression and consequently decrease ACE and ACE-2 concentrations. This shows that there are available agents able to act with a different modulation of RAS expression and its components. These evidences suggest that RAS could be modulated with a pharmacological approach to avoid complications of viral infection. There is a scientific debate (still ongoing) for several months as to whether increased ACE-2 using ACEIs or ARBs could be a risk factor for COVID-19 infection, at the moment epidemiological data do not show any correlation between the use of ACEIs or ARBs and increased likelihood of infection or complications of SARS-CoV-2. However, an increase in ACE-2 in the more severe stages of viral infection could be beneficial. An increase in ACE-2 synthesizes more Ang 1–7 and Ang-1-9 with vasodilating, antinfiammatory and antifibrotic properties (Schindler et al., 2007; Imai et al., 2005). In addition, the use of ARBs, increases the stimulation of AT-2r by Ang II, with vasodilating antifibrotic and antioxidant effects.

In conclusion, there is currently no evidence which demonstrate that the use of ACEIs or ARBs should be discontinued in treated patients, because they do not represent a risk factor that increases the likelihood of SARS-CoV-2 infection (Mancia et al., 2020), however it has been shown that the activation of the Ang II-AT-1r axis can promote lung damage, while increasing ACE-2 and activating the Ang 1–7/MASr axis may protect against lung damage (Kuster et al., 2020; European Society of Hypertension, 2020). RAS modulating agents may be beneficial in combating SARS-CoV-2 infection, clinical studies are necessary to confirm these hypotheses.

4. Suggestions

More extensive epidemiological studies should be designed to investigate the real correlation between RAS and COVID-19, in particular to clarify whether an increase of ACE-2 with ACEis or ARBs can be considered an important risk factor of SARS-CoV-2 infection, and whether an increase of ACE-2 in the most severe stages of infection can play a protective role, we believe based on current evidence in the literature that modulating the RAS system at the right time and correctly could be of enormous clinical benefit to avoid serious complications from COVID-19.

Main statements

I, The undersigned, Francesco Ferrara and any other author, declare that:

We have no conflict of interest;

We have not received funding;

There are no sensitive data and no patients were recruited for this study;

The document does not conflict with ethical legislation.

All authors read and approved the final manuscript.

Founds

None.

Copyright

The authors certify that the manuscript is original, never submitted to other journal for publication before. All authors contributed equally to the manuscript and had the opportunity to revise and approve the final text.

Disclosure statement

Dr. A. Vitiello has nothing to disclose.
Dr. F. Ferrara has nothing to disclose.

Declaration of competing interest

None of the Authors have conflicts of interest to disclose.

CRediT authorship contribution statement

Antonio Vitiello: Conceptualization, Writing - original draft, Methodology, Writing - original draft. **Francesco Ferrara:** Writing - review & editing, Supervision, Validation.

References

Atlas, S.A., 2007. The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic inhibition. J. Manag. Care Pharm. 13, 9–20. https://doi.org/10.18553/jmcp.2007.13.s8-b.9.

Bavishi, C., Bangalore, S., Messerli, F.H., 2016. Renin angiotensin aldosterone system inhibitors in hypertension: is there evidence for benefit independent of blood pressure reduction? Prog. Cardiovasc. Dis. 59, 253–261. https://doi.org/10.1016/j.pcad.2016.10.002.

Bavishi, C., Maddox, T.M., Messerli, F.H., 2020. Coronavirus disease 2019 (COVID-19) infection and renin angiotensin system blockers. JAMA Cardiol. https://doi.org/10.1001/jamacardio.2020.1282.

Chen, Q., Yang, Y., Huang, Y., Pan, C., Liu, L., Qiu, H., 2013. Angiotensin-(1-7) attenuates lung fibrosis by way of Mas receptor in acute lung injury. J. Surg. Res. 185, 740–747. https://doi.org/10.1016/j.jss.2013.06.052.

European Society of Hypertension, 2020. Statement of the European Society of Hypertension (ESH) Hypertension, the Renin–Angiotensin System, and the Risk of Lower Respiratory Tract Infections and Lung Injury: Implications for COVID-19. https://doi.org/10.1093/cvr/cvaa097.

Fang, C., Stavrou, E., Schmaier, A.A., Grobe, N., Morris, M., Chen, A., Nieman, M.T., Adams, G.N., LaRusch, G., Zhou, Y., Bilodeau, M.L., Mahdi, F., Warnock, M., Schmaier, A.H., 2013. Angiotensin 1-7 and Mas decrease thrombosis in Bdkrb2-/- mice by increasing NO and prostacyclin to reduce platelet spreading and glycoprotein VI activation. Blood 121, 3023–3032. https://doi.org/10.1182/blood-2012-09-459156.

Fang, L., Karakiulakis, G., Roth, M., 2020. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir. Med. https://doi.org/10.1016/S2213-2600(20)30116-8. S2213–2600.

Ferrario, C.M., Jessup, J., Chappell, M.C., Averill, D.B., Brosnihan, K.B., Tallant, E.A., Debra, I.D., Gallagher, P.E., 2005. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 111, 2605–2610. https://doi.org/10.1161/CIRCULATIONAHA.104.510461.

Fraga-Silva, R.A., Costa-Fraga, F.P., De Sousa, F.B., Alenina, N., Bader, M., Sinisterra, R. D., Santos, R.A., 2011. An orally active formulation of angiotensin-(1-7) produces an antithrombotic effect. Clinics 66, 837–841. https://doi.org/10.1161/HYPERTENSIONAHA.113.01274.

Fraga-Silva, R.A., Pinheiro, S.V., Goncalves, A.C., Alenina, N., Bader, M., Santos, R.A., 2008. The antithrombotic effect of angiotensin-(1-7) involves mas-mediated NO release from platelets. Mol. Med. 14 https://doi.org/10.2119/2007-00073, 28-3.

Guoping, L., Xiang, H., Lei, Z., Qin, R., Junyi, W., Anying, X., Dehong, W., Feng, C., Jinlyu, S., Christopher, C., 2020. Assessing ACE2 expression patterns in lung tissues in the pathogenesis of COVID-19. J. Autoimmun. 13, 102463. https://doi.org/10.1016/j.jaut.2020.102463.

Gurwitz, D., 2020. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev. Res. 2–5. https://doi.org/10.1002/ddr.21656.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395, 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.

Imai, Y., Kuba, K., Rao, S., Huan, Y., Guo, F., Guan, B., 2005. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 436, 112–116. https://doi.org/10.1038/nature03712, 2005.

Kuster, G.M., Pfister, O., Burkard, T., Zhou, Q., Twerenbold, R., Haaf, P., 2020. SARS-CoV2: should inhibitors of the renin–angiotensin system be withdrawn in patients with COVID-19? Eur. Heart J. 41 (19), 1801–1803. https://doi.org/10.1093/eurheartj/ehaa235, 14.

Lee, Y.B., Nagai, A., Kim, S.U., 2002. Cytokines, chemokines, and cytokine receptors in human microglia. J. Neurosci. Res. 69, 94–103. https://doi.org/10.1002/jnr.10253.

Magalhaes, G.S., Rodrigues-Machado, M.G., Motta-Santos, D., Silva, A.R., Caliari, M.V., Prata, L.O., Abreu, S.C., Rocco, P.R., Barcelos, L.S., Santos, R.A., Campagnole-Santos, M.J., 2015. Angiotensin-(1-7) attenuates airway remodelling and hyperresponsiveness in a model of chronic allergic lung inflammation. Br. J. Pharmacol. 172, 2330–2342. https://doi.org/10.1111/bph.13057.

Mancia, G., Rea, F., Ludergnani, M., Apolone, G., Corrao, G., 2020. Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19 NEJ. https://doi.org/10.1056/NEJMoa2006923.

Meng, Y., Yu, C.H., Li, W., Li, T., Luo, W., Huang, S., Wu, P.S., Cai, S.X., Li, X., 2014. Angiotensinconverting enzyme 2/angiotensin-(1-7)/Mas axis protects against lung fibrosis by inhibiting the MAPK/NF-kappaB pathway. Am. J. Respir. Cell Mol. Biol. 50, 723736. https://doi.org/10.1165/rcmb.2012-0451OC.

Nehme, A., Zouein, F.A., Zayeri, Z.D., Zibara, K., 2019. An update on the tissue renin angiotensin system and its role in physiology and pathology. J. Cardiovasc. Dev. Dis. 6 (2), 14. https://doi.org/10.3390/jcdd6020014.

Pai, W.Y., Lo, W.Y., Hsu, T., Peng, C.T., Wang, H.J., 2017. Angiotensin-(1-7) inhibits thrombin induced endothelial phenotypic changes and reactive oxygen species production via NADPH oxidase 5 downregulation. Front. Physiol. 8, 994. https://doi.org/10.3389/fphys.2017.00994.

Recinos, A., LeJeune, W.S., Sun, H., Lee, C.Y., Tieu, B.C., Lu, M., Hou, T., Boldogh, I., Tilton, R.G., Brasier, A.R., 2006. Angiotensin II induces IL-6 expression and the Jak-STAT3 pathway in aortic adventitia of LDL receptor-deficient mice. Atherosclerosis 194, 125–133. https://doi.org/10.1016/j.atherosclerosis.2006.10.013.

Schindler, C., Bramlage, P., Kirch, W., Ferrario, C.M., 2007. Role of the vasodilator peptide angiotensin-(1–7) in cardiovascular drug therapy. Vasc. Health Risk Manag. 3, 125–137.

Vaduganathan, M., Vardeny, O., Michel, T., McMurray, J.J.V., Pfeffer, M.A., Solomon, S. D., 2020. Renin–angiotensin–aldosterone system inhibitors in patients with COVID-19. N. Engl. J. Med. https://doi.org/10.1056/NEJMsr2005760.

Watkins, J., 2020. Preventing a COVID-19 pandemic. BMJ 368, 1–2. https://doi.org/10.1136/bmj.m810.

Wu, Y., 2020. Compensation of ACE2 function for possible clinical management of 2019-nCoV-Induced acute lung injury. Virol. Sin. https://doi.org/10.1007/s12250-020-00205-6.

Yamamoto, S., Yancey, P.G., Zuo, Y., Ma, L.J., Kaseda, R., Fogo, A.B., Ichikawa, I., Linton, M.F., Fazio, S., Kon, V., 2011. Macrophage polarization by angiotensin II-type 1 receptor aggravates renal injury-acceleration of atherosclerosis. Arterioscler. Thromb. Vasc. Biol. 31, 2856–2864. https://doi.org/10.1161/ATVBAHA.111.237198.

Zhang, H., Penninger, J.M., Li, Y., Zhong, N., Slutsky, A.S., 2020. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med. https://doi.org/10.1007/s00134-020-05985-9.

Zheng, Y.Y., Ma, Y.T., Zhang, J.Y., Xie, X., 2020. COVID-19 and the cardiovascular system. Nat. Rev. Cardiol. Springer US. Nat. Rev. Cardiol. 259–260. https://doi.org/10.1038/s41569-020-0360-5.

Zhou, P., Yang, X.L., Wang, X.G., Hu, B., Zhang, L., Zhang, W., Si, H.R., Zhu, Y., Li, B., Huang, C.L., 2020. Discovery of a novel coronavirus associated with the recent pneumonia outbreakinhumans and its potential bat origin. Nature 579, 270–273. https://doi.org/10.1101/2020.01.22.914952.