What do we know about the correlation between RAS and SARS-Cov-2 infection?

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Abstract

The first cases of patients infected with SARS-Cov-2 virus were recorded in China in November 2019, and then rapidly spread to all countries around the world, causing a global pandemic. Much is known about the pathophysiology of this virus infection, but perhaps not enough. One of the aspects still to be investigated is the correlation between the renin-angiotensin system (RAS) and SARS-Cov-2 infection. RAS is a physiological system with a key role in regulating the different functions of the human body. SARS-CoV-2, uses the enzyme ACE-2 as a potential factor of cell penetration and infectivity, moreover in the different stages of infection a functional variation of the RAS system has been noted in different targets and at different times. In particular, in this article, we discuss the role of RAS on SARS-Cov-2 infection, and possible therapies that acting modifiers the system.
Keywords: RAS, Sars-CoV-2, *infection, ACE-2, Renin, Coronavirus, Pharmacology*

Introduction

A new Coronavirus, (SARS-Cov-2) has been identified as the causative agent of Severe Acute Respiratory Syndrome (SARS), a severe form of viral pneumonia associated with high mortality, which has rapidly spread from China to the world with such severity that it has been described by the World Health Organization as a "global emergency".
SARS-CoV-2 , is an RNA virus that shares about 80% of the viral genome with SARS-COV (responsible for the 2003 outbreak).
Several studies have confirmed that the virus is able to penetrate into human cells by binding to the protein ACE2, the angiotensin 2 conversion enzyme, and being part of the RAS system, considered as a possible membrane receptor, it has also been noted that patients infected by the virus, have during the sick days functional variations in the concentrations of enzymes that are part of the RAS system, it is a defense mechanism of the human host that helps in the defense against infection, or is responsible for a worsening of clinical conditions and in this case pharmacologically correct? (1-3).

The Role of RAS

The renin angiotensin system (RAS) is a physiological mechanism that regulates different functions in the body, in particular the most important one is the regulation of blood pressure, the volume of circulating plasma (volaemia) and the tone of the arterial muscles through different mechanisms. RAS is an enzymatic cascade, the main route is plasma renin that converts angiotensinogen, released by the liver, into angiotensin I. Angiotensin I (Ang I) is subsequently converted to angiotensin II (Ang II) by the angiotensin conversion enzyme ACE. There is also another enzyme pathway, mediated by the conversion enzyme ACE-2.
ACE-2 is a type I transmembrane metallocarboxyptidase with ACE homology. The functions of ACE and ACE-2 are distinct. In fact, unlike ACE, which converts angiotensin I to angiotensin II, ACE-2 converts Ang II to Ang 1-7 and Ang I to Ang 1-9. In addition, the two enzymes are also expressed differently in tissues. For example, ACE2 is expressed more in tissues such as renal, cardiovascular and gastrointestinal tissues. ACE2 is in fact present in lung epithelial cells, intestinal enterocytes and blood vessel endothelial cells.
We do not yet know everything about the various stages of SARS-Cov-2 infection, but several studies have shown that the RAS system can be very much related to SARS-Cov-2 infection, and above all involved in all stages. SARS-Cov-2 infection has in fact been divided by experts in the field into three phases, the first asymptomatic or mildly symptomatic, the second and the most serious, which risk hospitalisation and in the worst cases oxygen support. In phase two and three it seems that the worst damage is caused by a local inflammatory state in the lungs and generalized to all systems.
First of all, ACE-2 has been identified as an input membrane receptor for SARS-CoV-2 in epithelial lung cells, this evidence may suggest that having increased expression of ACE-2 may increase the risk of contracting SARS-Cov-2.

In addition, variations in RAS have been shown, in the first 24h an activation of the system and then a decrease, although these variations do not follow a linearity between patient and patient, and in timing.
Certainly, RAS system activation is known to vary in conditions such as COPD, asthma, during viral infections and in smokers, demonstrating that the system is related to proper lung and airway function. The evidence suggests that the physiological balance of the RAS system and especially between ACE/ACE2 is likely to be altered by SARS-CoV-2 viral infection. This imbalance of the RAS system is likely to play a pathogenic role in lung injury and inflammatory mediator activation, but there is currently no certainty. Based on this assumption, ACE2 compensation and ACE/ACE2 function balancing could be a way to alleviate severe virus-induced lung injury.
The angiotensin 2 conversion enzyme (ACE-2) has been shown to play a role in fibrogenesis and inflammation of many organs, including the lungs. Studies in patients infected with SARS-Cov-2 have shown that 24 hours after SARS-CoV infection, ACE2 expression increases dramatically compared to expression at 12h, before being rapidly down-regulated in lung tissue when the patient enters phase two and three of the infection. However, one might then think that ACE-2 has a protective effect, and when it decreases it worsens the inflammatory state of the lungs. In addition, there are studies showing that ACE-2 expression is decreased in respiratory diseases such as pulmonary fibrosis or COPD. This description might suggest that a modulation in the different stages of RAS infection could be beneficial and effective therapy. (4-12)

Adjusting the RAS system in SARS-COV-2

When it will be possible to understand definitively, if and above all how the RAS system varies in the various stages of SARS-Cov-2 infection, it will be possible to act pharmacologically to modulate the system.
In fact, depending on their biological target, drugs acting on the RAS system can be distinguished as angiotensin conversion enzyme ACE (ACE-I) inhibitors, angiotensin II receptor blockers (ARB) and direct renin inhibitors (DRI).
These drugs are currently indicated for the treatment of various cardiovascular diseases.
ACE-I lowers blood pressure by blocking the enzyme ACE which hydrolyzes angiotensin I into angiotensin II. In addition, by blocking ACE, there is less metabolisation and inactivation of bradykinin, a vasodilator peptide. ARBs are Ang II antagonists on the type 1 receptor (AT1). Finally, ARBs block plasma renin activity and inhibit the conversion of angiotensinogen to angiotensin 1.
The three different classes described above have different effects on counter regulation and enzyme expression in the RAS system. In fact, from in vitro studies, it seems that the use of ACE-i, by blocking the enzyme ACE, increases the expression of the enzyme ACE-2 (by stimulating other pathways of synthesis), although these data are not fully confirmed, and at the moment very contradictory.
The use of Ang II antagonists appears to be linked to a slight increase in the expression of both ACE and ACE2. Finally, the use of renin blockers, inhibiting the upstream RAS cascade, seems to inhibit expression and thus decrease ACE and ACE-2 concentrations. This shows that agents that act differently by modulating the expression of RAS and its enzymatic protagoonists in different ways are available, when more information will be available on the proper management of the RAS system and how to modulate it pharmacologically to avoid a worsening of the clinical condition of a patient infected with SARS-CoV-2, or even better to decrease the risk of infection (by acting by decreasing the expression of ACE-2), the scientific world will have taken a big step forward.
At the moment there are no certain data, and it is not advisable to suspend treatments for cardiovascular diseases already in progress, with the drugs indicated above. (12-21)

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.

Regards

The authors

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