Potential pharmacological approach in the regulation of ACE-2 and DPP-IV in diabetic COVID-19 patient

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Abstract

The global pandemic caused by COVID-19 has caused more than 1 million deaths worldwide. Some vaccines in clinical trials have reached stage 3. In the meantime, the understanding of the biological and pathophysiological mechanisms of Sars-CoV2 infection is still unclear, such as the role that ACE-2 and DPP-IV may play in patients with diabetes related to COVID-19. The individual with diabetes is a known COVID-19 risk patient. Probably the pharmacological regulation of the RAS system and of ACE-2 on the one hand, and of the incretin system and DPP-IV on the other, could represent a therapeutic route of fundamental importance to reduce the risk of Sars-CoV-2 infection or of serious complications caused by infection.

The COVID-19 global pandemic

Since March 2020, the world is facing a pandemic caused by a new Coronavirus (SARS-CoV-2) responsible for Coronavirus disease (COVID-19), a viral infection that can in some cases cause severe acute respiratory syndrome associated with multisystemic inflammation and tissue damage. To date, the virus has caused over 1 million deaths worldwide. (1) Effective vaccines are being tested. (2) Some risk factors for COVID-19 infection and mortality have been identified, including pulmonary diseases, cardiovascular system diseases, metabolic diseases such as diabetes. (3)

SARS-CoV-2 correlation with ACE-2 and DPP-IV

ACE-2 has a fundamental function in the angiotensin renin (RAS) system, as it metabolises Ang II into Ang-(1-7) and Ang I into Ang-(1-9) which in turn is metabolised as Ang-(1-7) by the angiotensin conversion enzyme (ACE). Ang-(1-7) from MASr opposes the effects induced by Ang II from AT1r. The effects of Ang-(1-7) are vasodilator, anti-inflammatory, antioxidant, antiproliferative and antithrombotic. (4) DPP4 is a serine exopeptidase that causes rapid cleavage of the active AQA-1 almost immediately after its secretion, with a half-life of 1-2min. The angiotensin-II conversion enzyme (ACE2) has been shown to be an entry receptor for SARS-CoV-2 cells. (5) However, it
appears that in cell adhesion and cell penetration other proteins are crucial for the entry action of the virus. Some experiments have suggested that SARS-CoV-2 could also use dipeptidil 4 peptidil 4 (DPP-IV) as an entry receptor for cells. (6) It appears that the interaction between the SARS-CoV-2 glycoprotein peak and human DPP-IV is a key factor for hijacking and virulence. Changes in levels of soluble ACE-2 and DPP-IV are reported to be clinically relevant in a number of diseases, particularly diabetes (7). In addition, a change in ACE-2 has also been reported during COVID-19 infection, in particular a decrease in concentration in the most severe stages. (8) It will be important to investigate whether and how changes in ACE-2 and DPP-VI in patients with diabetes influence the risk of COVID-19 infection or mortality, also considering the protective role of ACE-2 against COVID-19 lung lesions. Patients with diabetes may be at increased risk for several reasons, such as a compromised immune system, dysregulated coagulation/fibrinolytic cascade, or due to the increased presence of ACE-2 and DPP-IV which may contribute to an increased presence of SARS-CoV-2 cell entry receptors. Probably the role of ACE-2 and DPP-IV is fundamental in the course of COVID-19 infection in patients with diabetes, and in this direction we can consider the enormous importance of the therapeutic potential of RAS modifying drugs and DPP-IV inhibitors.

**Therapeutic strategies acting on ACE-2 and DPP-IV**

Given the importance of ACE-2 and DPP-IV in COVID-19 pathophysiology, a potential pharmacological approach is represented by agents able to act on ACE-2 and DPP-IV. Considering the possible mechanisms of intracellular penetration of SARS-CoV-2 described above, the significant related risk factors, changes in ACE-2 concentration, increased expression of DPP-IV in patients with diabetes and COVID-19, modulation of RAS and ACE-2 and DPP-IV at certain stages of infection could be considered an important therapeutic strategy. In particular, the loss of ACE-2 function observed in the most severe stages of infection, and consequent non-activation of the Ace-2/Ang-(1-7) MASr axis and hyperstimulation of the Ace/Ang-2/ AT1r axis may be co-responsible for the pathophysiological mechanisms leading to tissue lesions. An increase in ACE-2 with RAS modifying
drugs such as ACEi or ARB could be a viable therapeutic option in the severe stages of infection. (9) An increase in DPP-IV appears to be related instead to a potential increased amount of cell entry receptor, and an increase in pro-inflammatory cytokines. Some evidence shows that DPP-IV could directly influence the kinetics of pulmonary inflammation and could itself act as a pro-inflammatory molecule. Inhibition of DPP-IV with gliptins could antagonise this mechanism. Inhibition of DPP-IV by gliptins could antagonise cell entry and virulence of SARS-CoV-2 and acute multi-organ damage by means of several additional effects such as cytokine reduction reduction of macrophage activity/function enhancement of GLP-1 anti-inflammatory activity especially in severe patients COVID-19 (10) (11) (12) (Figure 1).

Risks

The association of an ACEi and gliptins could represent a potential pharmacological synergy, however there are risks. ACE and DPP-IV are proteases with a metabolizing action of bradykinin and P substance. Excessive concentration of bradykinin could worsen through B2 receptors stimulating inflammation of the respiratory tract of the COVID-19 subject. (13)

Conclusions and suggestions

Patients with diabetes are more at risk of COVID-19 severity. While waiting for effective vaccines, it is urgent to identify the best therapeutic strategies for this category of patients. In patients with diabetes and COVID-19 infection there may be an alteration in the expression of RAS, ACE-2, DPP-IV. Pharmacological strategies aimed at regulating these mediators could represent a therapeutic potential. Well-structured clinical studies are necessary to generate evidence on this interesting topic.

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Figure 1. DPP-IV inhibition leads to an increase in GLP-1 which causes a decrease in the activation of the proinflammatory transcription factor NF-kB.