Potential pharmacological approach in the regulation of angiotensin-II conversion enzyme and dipeptidyl-peptidase 4 in diabetic COVID-19 patients

Francesco Ferrara,[1] Antonio Vitiello[2]

[1]Hospital Pharmacist Manager, Pharmaceutical Department, Usl Umbria 1; [2]Clinical Pharmacologist, Pharmaceutical Department, Usl Umbria 1, Perugia, Italy

ABSTRACT

The global pandemic caused by coronavirus disease 2019 (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 biological and pathophysiological mechanisms of severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) infection is still unclear, such as the role that angiotensin-II conversion enzyme (ACE-2) and dipeptidyl-peptidase 4 (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 angiotensin renin system and ACE-2 on the one hand, and of the incretin system and DPP-IV on the other hand, could represent a therapeutic route of fundamental importance to reduce the risk of SARS-CoV-2 infection or of severe complications caused by infection.

The COVID-19 global pandemic

Since March 2020, the world is facing a pandemic caused by a new coronavirus disease 2019 (COVID-19) responsible for a severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) infection, 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, cadiovascular system diseases, metabolic diseases such as diabetes.[3]

Correspondence: Francesco Ferrara, Hospital Pharmacist Manager, Pharmaceutical Department, Usl Umbria 1, via A. Migliorati, 06132 Perugia, Italy.
E-mail: francesco.ferrara@uslumbria1.it

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SARS-CoV-2 correlation with angiotensin-II conversion enzyme and dipeptidyl-peptidase 4

Angiotensin-II conversion enzyme (ACE-2) has a fundamental function in the angiotensin renin (RAS) system, as it metabolizes Ang II into Ang-(1-7) and Ang I into Ang-(1-9), which in turn is metabolized as Ang-(1-7) by the 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] Dipeptidyl-peptidase 4 (DPP-IV) is a serine exopeptidase that causes rapid cleavage of the active AQA-1 almost immediately after its secretion, with a half-life of 1-2 min. The ACE-2 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 DPP-IV as an entry receptor for cells.[6] It appears that the in-

teraction between the SARS-CoV-2 glycoprotein peak and human DPP-IV is a key factor for the hijacking and virulence. Changes in soluble ACE-2 and DPP-IV levels are reported to be clinically relevant in some 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 the increased presence of ACE-2 and DPP-IV, which may contribute to an increased presence of SARS-CoV-2 cell entry receptors. The role of ACE-2 and DPP-IV is probably fundamental in the course of COVID-19 infection in patients with diabetes. We can consider the enormous importance of the therapeutic potential of RAS modifying drugs and DPP-IV inhibitors in this direction.

Therapeutic strategies acting on angiotensin-II conversion enzyme and dipeptidyl-peptidase 4

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 ACE inhibitors (ACEi) or ARB could be a viable therapeutic option in the severe infection stages.[9] Instead, an increase in DPP-IV appears to be related to a possible 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 antagonize this mechanism. Inhibition of DPP-IV by gliptins could antagonize 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 glyptin-1 anti-inflammatory activity especially in severe patients COVID-19[10-12] (Figure 1).

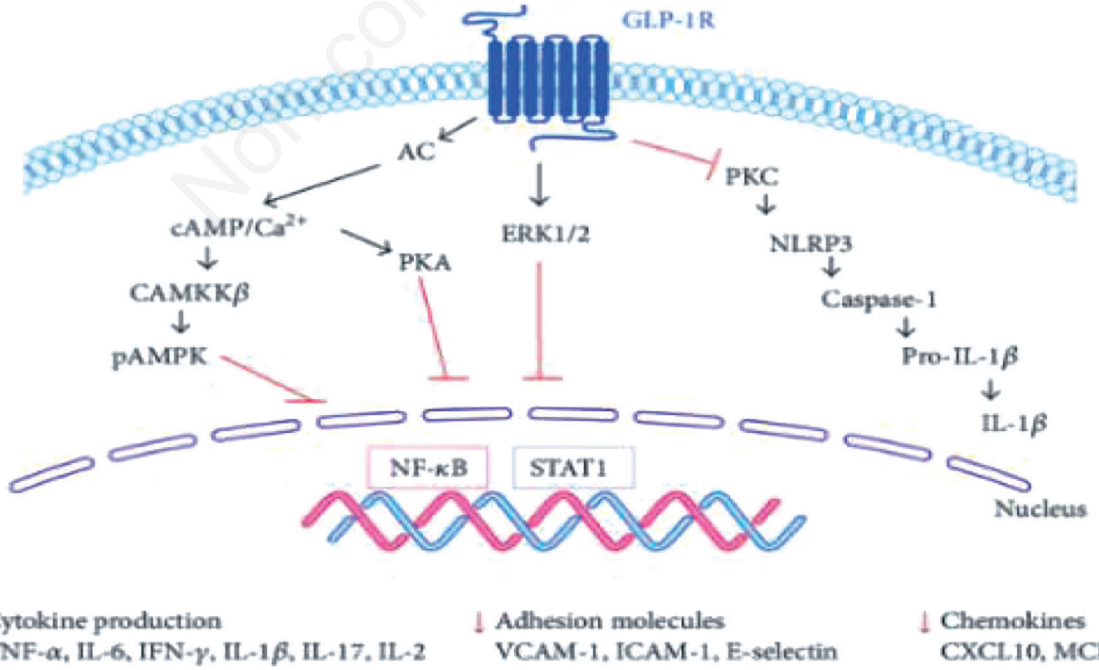

Figure 1. Dipeptidyl-peptidase 4 inhibition leads to an increase in glyptin-1 (GLP-1), which causes a decrease in the activation of the proinflammatory transcription necrosis factor (NF)-kB.

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 bradykinin concentration 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 RAS, ACE-2, and DPP-IV expression. 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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