MINI REVIEW

SARS-CoV-2 perturbs the renin-angiotensin system and energy metabolism

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INTRODUCTION

The current COVID-19 pandemic, caused by the novel coronavirus, SARS-CoV-2, is severely compromising health care systems worldwide and altering the course of our daily lives. Despite the infected individuals being treated, there is a rising concern that patients with chronic diseases (including cardiovascular diseases, hypertension, diabetes mellitus, and severe obesity) have an increased risk of severe SARS-CoV-2 infections. This notion is based on the fact that these comorbidities are most frequent in patients with severe SARS-CoV-2 infections (5, 20, 34). Diabetes mellitus is an independent risk factor for the severity of SARS-CoV-2 infections (6). Angiotensin-converting enzyme 2 (ACE2) has received much attention during this COVID-19 pandemic, owing to the fact that SARS-CoV-2 uses ACE2 as a receptor for cellular entry. Additionally, the RAS greatly affects energy metabolism in certain pathological conditions, including cardiac failure, diabetes mellitus, and viral infections. This article discusses the potential mechanisms by which SARS-CoV-2 modulates the RAS and energy metabolism in individuals with obesity and diabetes mellitus. The article aims to highlight the appropriate strategies for combating the COVID-19 pandemic in the clinical setting and emphasizes on the areas that require further investigation in relation to COVID-19 infections in patients with obesity and diabetes mellitus from the viewpoint of endocrinology and metabolism.

energy metabolism; obesity; RAS; SARS-CoV-2

zolidinediones also upregulate the expression and/or function of ACE2 (27, 36). Therefore, there has been a rising concern regarding the administration of drugs that upregulate the expression of ACE2 to patients with COVID-19. Despite such theoretical concerns, the clinical data as to whether ACEIs and ARBs increase susceptibility of SARS-CoV-2 is lacking, and these drugs are clearly beneficial for the patients with cardiac disease, chronic kidney disease, and hypertension (28). Several scientific societies, including the American College of Cardiology, the American Heart Association, and the American Society of Hypertension, have recommended the continued use of these drugs in patients with COVID-19 infections (2). The COVID-19 pandemic has caused turmoil in the clinical scenario and imposes as an additional challenge to patients with endocrine diseases and diabetes. Endocrinologists need to understand the precise mechanism by which the renin-angiotensin system (RAS), including ACE2, interacts with SARS-CoV-2 for treating patients with endocrine diseases who are at an increased risk of SARS-CoV-2 infections. Understanding the mechanisms and physiology that increase the risk of SARS-CoV-2 infections is necessary for providing adequate therapy for patients with endocrine diseases and also for promoting both basic and clinical research in the field of endocrinology.

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and metabolism. This article discusses the mechanism by which SARS-CoV-2 affects the RAS and energy metabolism, especially in obesity patients, with or without diabetes.

THE INVOLVEMENT OF THE RAS IN SARS-CoV-2 INFECTIONS

The classical RAS is a hormonal system that regulates blood pressure as well as fluid and electrolyte homeostasis. Angiotensinogen, the principal precursor of the RAS, is produced from the liver and is sequentially cleaved into angiotensin I (Ang I) and angiotensin II (Ang II) by renin and ACE, respectively.

ACE2, located on the surface of endothelial cells, is a carboxypeptidase that hydrolyzes Ang I (Ang 1–10) and Ang II (Ang 1–8) to Ang 1–9 and Ang 1–7, respectively (23). Ang II mediates its physiological effects through the G protein-coupled receptors angiotensin II type 1 receptor (AT1R) and angiotensin II type 2 receptor (AT2R). The primary effects of Ang II, including inflammation, vasoconstriction, fibrosis, and the production of reactive oxygen species (ROS), are mediated via AT1R (Fig. 1). Additionally, ACE2 counteracts the ACE-Ang II-AT1R axis via the Mas receptor, which is specific to Ang 1–7 (Fig. 1). ACE2 has numerous beneficial effects, including cardioprotective, nephroprotective, antidiabetic, and antioxidative effects (9, 21, 22, 37). The binding of Ang 1–7 to the Mas receptor mediates the activation of phosphatidylinositol kinase (PI3K), which subsequently alters the immune system by upregulating the phosphatidylinositol signaling pathway (12, 18).

The balance between ACE/Ang II/AT1R and ACE2/Ang 1–7/MasR is crucial for maintaining normal health (30). ADAM17 plays a key role in maintaining the balance between ACE/Ang II/AT1R and ACE2/Ang 1–7/MasR by mediating the shedding of the ectodomain of ACE2.

ACE2 plays a crucial role in viral entry into host cells and subsequent viral proliferation, as the SPIKE protein (S protein), located on the viral coat of SARS-CoV-2, binds ACE2 and mediates cellular entry (Fig. 2) (29). ACE2 is ubiquitously expressed, and the expression of ACE2 is highest in the gut, kidneys, adipose tissue, heart, and lungs (38). The ubiquitous expression of ACE2 is consistent with various symptoms of SARS-CoV-2 infections, such as respiratory symptoms, gastrointestinal symptoms, acute cardiac damage including arrhythmia, liver, and kidney damage (4, 35). Some studies have warned against the usage of ACE2 stimulating drugs, including ACEIs and ARBs, and recommend the discontinuation of these drugs. On the other hand, in diabetic patients, the expression of the ACE2 protein is increased in the kidneys, lungs, heart, and pancreas (14, 26, 32), indicating that the expression of ACE2 is upregulated regardless of drug intake. The upregulation in the expression of ACE2 could be associated with the increased susceptibility of obese and diabetic individuals to SARS-CoV-2 infections, since SARS-CoV-2 enters the cell by binding to ACE2. However, we cannot simply say the upregulation of ACE2 is detrimental. ACE2 serves as an alternative protective arm of the ACE2-Ang1–7-Mas receptor axis, which counteracts the ACE-Ang II-AT1 receptor axis that is activated under pathological conditions. The initial detrimental effects of viral infections result from a loss of the protective effects of ACE2 (31). An increase in the levels of Ang II triggers vasoconstriction, inflammation, cell proliferation, and fibrosis. ACE2 cleaves Ang II into Ang 1–7, which induces the counteractive effect of the Ang II-AT1 receptor axis via the Mas receptor. The ACE2-Ang 1–7-Mas receptor axis has two pathways, one of which decreases the levels of Ang II, and the other which induces the counteractive effects of the Ang II-AT1 receptor axis (4). ACE2 is not only an entry receptor for the SARS-CoV-2 virus but also protects against the pathogenic effects of RAS and the ACE-Ang II-AT1R axis.

Obese subjects, with or without diabetes, have a defective immune response owing to chronic inflammation (1). In fact, obesity was reported to be an independent risk factor for hospitalization and death due to the H1N1 Influenza A virus (13). The production of Ang II and several proinflammatory cytokines, including TNFα, monocyte chemoattractant protein-1 (MCP-1), and IL-6 is higher in obese patients than in normal individuals (24). Both Ang II and proinflammatory cytokines are primarily regulated by ADAM17, a type I transmembrane metalloproteinase. The expression of ACE2 in tis-

Fig. 1. Balance between the angiotensin-converting enzyme (ACE)-angiotensin II (Ang II)-angiotensin I receptor (AT1R) axis and the ACE2-Ang 1–7-Mas receptor axis. A: ACE2 converts Ang II to Ang 1–7. B: Ang II binds to AT1R and induces numerous detrimental effects, including vasoconstriction, production of reactive oxygen species (ROS), hypertrophy, and fibrosis. C: Ang 1–7 binds to the Mas receptor and induces protective effects and counteracts the ACE-Ang II-AT1R axis. D: ADAM17 mediates the shedding of the ectodomain of ACE2.
sues is upregulated in response to an increase in the levels of Ang II, and ACE2 functions as the protective arm of the ACE2-Ang 1–7-Mas receptor axis. Viral endocytosis increases the activity of ADAM17, which results in the shedding of the ectodomain of ACE2 on the cell surface. This leads to a shift from the ACE2-Ang 1–7-MasR axis to the ACE-Ang II-AT1R axis. This shift augments RAS effects on various pathological conditions, including inflammation and the production of ROS. Another potential mechanism increasing the susceptibility for SARS-CoV-2 in patients with diabetes is proposed, such as impaired T cell function and susceptibility to elevated cytokines. Obesity also alters T cell response to viral infection. RAS-involved production of cytokines and impaired immune system might increase susceptibility to SARS-CoV-2 in obese individuals with or without diabetes.

SARS-CoV-2 INFECTIONS AFFECT ENERGY METABOLISM

Viral infection in mammalian cells affects cellular metabolism by inducing a switch in the metabolism from oxidative phosphorylation to glycolysis, which decreases ATP production. For instance, the H1N1 viral infection decreases the activity of the pyruvate dehydrogenase complex (PDC) and ATP production by upregulating pyruvate dehydrogenase kinase 4 (PDK4), which is a critical player in regulating carbohydrate oxidation via PDC phosphorylation. In diabetes, the activity of PDC is decreased by PDK, which phosphorylates and inactivates PDC. Interestingly, Ang II causes insulin resistance by suppressing the activity of PDC via the phosphorylation and acetylation of PDC. The uncoupling between glycolysis and oxidative phosphorylation, that is,
glucose oxidation, produces protons via the hydrolysis of ATP derived from glycolysis, leading to intracellular acidosis and cellular dysfunction (17). Ang II also causes impaired mitochondrial function (17). Therefore, we hypothesize that SARS-CoV-2 infections induce an imbalance in the RAS, downregulate the ACE2-Ang I–7-MasR axis, and upregulate the ACE-Ang II-AT1R axis. The imbalance in the RAS reduces the activity of PDC, which subsequently perturbs energy metabolism in cells (Fig. 3). Obese individuals, with or without diabetes, have insulin resistance, which is associated with an increase in the activity of PDK that phosphorylates and inactivates PDH. Therefore, SARS-CoV-2 infections exacerbate the perturbation in energy metabolism in obese individuals with or without diabetes.

CONCLUSION

In addition to respiratory complications, SARS-CoV-2 infections induce multiorgan dysfunctions by perturbing the RAS and energy metabolism. Restoring the balance in the RAS and energy metabolism could be crucial to reducing disease severity and the mortality of patients with COVID-19, and especially obese patients, with or without diabetes. Further epidemiological investigations are necessary for clarifying whether the susceptibility to SARS-CoV-2 infections and the severity of COVID-19 is higher in obese individuals with or without diabetes in comparison with those of normal individuals. Furthermore, since the individuals affected during the SARS outbreak in 2002 have been reported to have a high risk of long-term endocrine sequelae (10), we need to investigate whether individuals infected with SARS-CoV-2 have endocrine sequelae.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

J.M., G.Y.O., and G.D.L. conceived and designed research; J.M. prepared figures; J.M. drafted manuscript; J.M.G.Y.O., and G.D.L. edited and revised manuscript; J.M., G.Y.O., and G.D.L. approved final version of manuscript.

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