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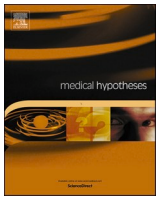

Potential therapeutic effect of glucagon-like peptide-1 receptor agonists on COVID-19-induced pulmonary arterial hypertension

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an infectious diseases caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Now, it is pandemic over the world. SARS-CoV-2 often causes a "cytokine storm" in people with COVID-19, causing inflammatory lung damage and pneumonia, which eventually leads to death. Glucagon like peptide-1 (GLP-1) is well known as an incretin hormone responsible for regulation of blood glucose through its receptor. Beyond glycemic control, GLP-1 receptor agonists (GLP-1RAs) have promising anti-inflammatory actions in human and rodent pathological models. Recent studies proved that GLP-1RAs attenuate pulmonary inflammation, reduce cytokine production, and preserve lung function in mice and rats with experimental lung injury. Moreover, a thickened pulmonary vascular wall, an important characteristic of pulmonary arterial hypertension (PAH) was observed in the autopsy lung tissue of a COVID-19 patient. Thus GLP-1RAs may be a novel therapeutic strategy for combating this pandemic specifically for patient characteristics of PHA after COVID-19 infection.

Introduction

In 2019, Coronavirus Infectious Disease-19 (COVID-19) originated in Wuhan, China and spread to the world through Hubei Province, China [1]. The severe acute respiratory syndrome (SARS)-CoV-2 is a novel coronavirus identified as the cause of COVID-19 [1,2]. It causes severe respiratory syndrome and a severe systemic inflammation thereby leading to death [3]. Since the beginning of the pandemic, the emergence of new strain of SARS-CoV-2 has been reporting in many other countries and it is a great threat to current vaccination strategies and to end the pandemic [4,5]. In addition, the number of people recovering from SARS-CoV-2 infection will be significant as more people are expected to be infected with the virus without an official diagnosis [6]. This population may be more likely to develop unknown disease sequelae for the rest of their life.

Tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interferon-γ (IFN-γ) are important pathogenic cytokines associated with aggressive inflammatory response and circulating IL-6 is an independent predictor of COVID-19 severity [7–9]. Cytokine storm in patients with COVID-19 is a leading cause of inflammatory lung damage, worsening pneumonia and death [10]. Therefore, effective management of cytokine storm is determinant for survival or death for COVID-19. Although the mortality rate is still high, many people recover from COVID-19 and return to their normal lives. However, some clinical studies have shown that signs of lung damage persist longer even when inflammatory biomarker levels normalize [11]. Moreover, post-mortem lung tissues from COVID-19 patients observed thickened pulmonary vascular walls, an important characteristic of pulmonary arterial hypertension (PAH) [12].

Glucagon like peptide-1 (GLP-1) is an incretin hormone released from the intestine and regulates blood glucose by stimulation of insulin secretion and suppression of glucagon secretion through its receptor in pancreas [13,14]. Beyond glycemic control, GLP-1 receptor agonists (GLP-1RAs) have promising anti-inflammatory actions in animal models and reduce levels of circulating proinflammatory biomarkers in human diabetic subjects and obese people [15,16]. Moreover, GLP-1RAs attenuate pulmonary inflammation, reduce cytokine production, and preserve lung function in mice and rats with experimental lung injury. Taken together, these studies indicate that GLP-1RAs may play beneficial effects not only in the treatment of COVID-19 patient characteristics of pulmonary arterial hypertension but also in suppression of systemic inflammatory responses.

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Testing the hypothesis

Apart from their glucose lowering effects, GLP-1RAs may have broadly beneficial effects for the treatment of patients, infected with COVID-19, with or without type 2 diabetes at least by suppressing inflammatory response named "cytokine storm". In addition, GLP-1RAs may be a particularly potential therapeutic candidate for PAH patients recovering or recovered from COVID-19 infection by regulating on right ventricular systolic pressure and pulmonary vascular remodeling.

Discussion

Despite some vaccines of COVID-19 have already been developed and vaccinations are rapidly being implemented in many countries, COVID-19 pandemic still is ongoing. Indeed, the root cause of the pessimism for ending this pandemic COVID-19 is the high mutation rate of SARS-CoV-2 and the lack of optimized drug/therapeutic approaches to date [5,17–19].

As multiple strains emerge, the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) independently established a classification system to classify new strains of SARS-CoV-2 into variants of concern (VOCs) and variants of interest (VOIs) [5,18,19]. Since the pandemic began, four of them were classified as VOCs including Alpha (B.1.1.7); Beta (B.1.351); and Gamma (P.1) and Delta (B.1.617.2). Seven variants (Epsilon [B.1.427 and B.1.429]; Zeta [P.2]; Eta [B.1.525]; Theta [P.3]; Iota [B.1.526]; Kappa [B.1.617.1] and Lambda [C.37]) belong to VOIs [5,18]. The emergence of these new strains of SARS-CoV-2 poses a new threat to stop the spread of this pandemic. Therefore, the development of potential therapeutic candidates and new vaccines specifically targeting these new strains is of greater importance to end this pandemic.

In spite of diverse beneficial roles of GLP-1 (such as anti-inflammatory and anti-obesogenic properties, and pulmonary protective effects), the use of GLP-1RAs in COVID-19 treatment is controversial [20], mainly because of its unstable therapeutic effects [21,22], and the ACE2 upregulation induced by GLP-1RAs [23]. However, cumulative studies have shown a more beneficial effect in managing COVID-19 patients with diabetes and those without diabetes [20]. Blood glucose at admission was considered an independent risk factor predicting the progression to severe or mild disease in patients with COVID-19 [24]. In addition, hyperglycemia, hypoglycemia, and high glucose variability significantly increased COVID-19 mortality [25,26]. These reports indicate that well-controlled blood glucose within a certain range will be a more important factor in lowering mortality from COVID-19. In particular, GLP-1RAs are effective in reducing hyperglycemia and glycemic variability without increasing the risk of hypoglycemia [27].

Pulmonary insufficiency is the leading cause of death in COVID-19 patients. Recently, Suzuki et al. reported that patients who died from COVID-19 showed thickened pulmonary vascular walls in postmortem lung tissues, an important characteristic of PAH [12]. Several studies have shown that GLP-1RAs improve lung function by reducing inflammation and cytokine production and mucus secretion in lung injury rodent models [28,29]. Moreover, Rogliani et al. recently reported that treatment with GLP-1RAs improves lung function regardless of the blood glucose levels, in diabetic patients, indicating that GLP-1RAs have a direct effect on lung tissue [30]. More recent study also showed reductions in respiratory complications and mortality by GLP-1RAs within 28 days following a COVID-19 diagnosis [31]. Since signs of lung damage last longer, people with a history of SARS-CoV-2 infection are more likely to develop PAH in their future. Therefore, apart from their lowering blood glucose effects, GLP-1RAs will be a new clinical option for the treatment of PAH at least due to its anti-inflammatory effects targeting lung tissue.

Although angiotensin-converting enzyme 2 (ACE2) enables virus entry into host target cells, ACE2 upregulation induced by GLP-1RAs may ameliorate lung injury during COVID-19 affecting on inflammatory and fibrotic processes [23]. In addition, ACE2 overproduction may counteract the decline in ACE2 expression levels characteristic of infection progression [32–34]. In line with these studies, overexpression of GLP-1 receptors suppressed cytokine release in chronic obstructive respiratory diseases [35]. Moreover, preclinical study indicated that GLP1-RAs reduce cytokine production and lung inflammation [28,29,36,37]. Recently, Kahkoska et al. showed that the 60-day mortality after positive SARS-CoV-2 PCR test was reduced by GLP-1RA [22]. Another study also showed that GLP-1-RAs do not increase the risk of respiratory tract infection and pneumonia in patients with type 2 diabetes and cardiovascular comorbidities [38], suggesting that it is a safe treatment option for COVID-19 patients.

In conclusion, all these exciting studies further suggest that the treatment of GLP-1RAs may be useful for not only suppressing hyperinflammatory response but also attenuating PAH clinically observed in COVID-19 patients. However, there is still insufficient clinical evidence to clarify the beneficial effects of GLP-1RAs on PAH associated with COVID-19. Therefore, the current hypothesis is more valuable and needs to be confirmed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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