Review Article

COVID-19 and Phosphodiesterase Enzyme Type 5 Inhibitors

Hayder M. Al-Kuraishy, Ali I. Al-Gareeb, Marwa S. Al-Niemi[1], Ali K. Al-Buhadily, Nasser A. Al-Harchan[2], Claire Lugnier[3]

Department of Clinical Pharmacology, Medicine and Therapeutic, Medical Faculty, College of Medicine, Al-Mustansiriyia University, [1]Department of Clinical Pharmacology, Medicine and Therapeutic, Medical Faculty, College of Medicine, Al-Farahedi University, [2]Department of Clinical Pharmacology, College of Dentistry, Al-Rasheed University, Baghdad, Iraq, [3]Department EA 3072 "Mitochondria, Oxidative Stress and Muscular Protection", Institute of Physiology, Faculty of Medicine, Strasbourg Cedex, France

Abstract

COVID-19 pathology is mainly associated to a pulmonary disease which sometimes might result in an uncontrollable storm related to inflammatory diseases which could be fatal. It is well known that phosphodiesterase enzyme type 5 inhibitors (PDE5Is), such as sildenafil, have been successfully developed for the treatment of pulmonary arterial hypertension; interestingly, more recently, it was shown that PDE5Is might be also anti-inflammatory. Therefore, it would be of interest to question about the use of PDE5Is to overcome the COVID-19 storm, as much as PDE5 is mainly present in the lung tissues and vessels.

Keywords: Acute lung injury, COVID-19, nucleotide phosphodiesterase enzyme

Background

In December 2019, a novel coronavirus (nCoV) was appeared in Wuhan city of China, named 2019-nCoV, leading to coronavirus infection disease (COVID-19), which causes severe acute respiratory syndrome (SARS). On January 20, 2020, the World Health Organization affirmed and declared the COVID-19 outbreak as an international health emergency, which was regarded as an epidemic on March 11, 2020.[1]

CoV is an enveloped positive-sense, single-strand RNA virus, which is the largest one among other RNA viruses from *Coronaviridae* family. CoV has three imperative proteins in its structure, which are membrane protein, spike protein, and nucleocapsid protein. These structural proteins are involved in the viral pathogenesis and regarded as targets for different experimental antiviral agents [Figure 1].[2]

Previously, human CoV (HCoV-OC43) and HCoV-229E were the only known coronaviruses, as HCoV-OC43 was isolated in 1967 from volunteers with the common cold in the United Kingdom. The analysis of genome sequences proposed that HCoV-OC43 was originated from bovine, so-called bovine CoV.[3] 2019-nCoV is a betacoronavirus which is officially known as SARS-CoV-2, which has about 80% nucleotide similarity with SARS-CoV.[4]

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Amide different recent researches, the entry point of SARS-CoV-2 is through angiotensin-converting enzyme type 2 (ACE2), which is highly expressed in the alveolar pulmonary cells, renal proximal tubules, and vascular endothelium. Besides, different peptides and comediators such as bradykinin, plasmin, and transmembrane serine protease may modulate the affinity and binding of SARS-CoV-2 to ACE2 [Figure 2].[5]

Horn *et al*. found that patients with pulmonary arterial hypertension (PHT) are at a higher risk for COVID-19-induced adverse outcomes and complications. Since infection with SARS-CoV-2 is linked with cardiovascular complications and acute respiratory distress syndrome (ARDS).[6]

Cyclic nucleotide phosphodiesterase enzyme (PDE) plays a major role in intracellular signaling by controlling beyond receptors' cellular responses.[7] Their specific PDE inhibitors (PDEIs) are drugs that overcome the hydrolytic inactivation of intracellular cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) in their respective 5' nucleotide. There

Address for correspondence: Prof. Hayder M. Al-Kuraishy, Department of Clinical Pharmacology, Medicine and Therapeutic, Medical Faculty College of Medicine, Al-Mustansiriya University, P O Box 14132, Baghdad, Iraq.
E-mail: hayderm36@yahoo.com

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are two types of PDEIs, nonspecific (theophylline, aminophylline, and pentoxifylline) and specific (nimodipine, rolipram, cilostazol, and sildenafil).[8] There are 11 subtypes of PDE family, however PDE4 is the chief cAMP-metabolizing enzyme found in the immune and inflammatory cells. Therefore, PDE4 inhibitors have been proven as anti-inflammatory agents against different pulmonary disorders through inhibiting the release of inflammatory signals and cytokines.[9] As well, all types of PDE type 5 inhibitors (PDE5Is) increase the level of nitric oxide (NO), which has potent antiviral effects, reducing the migration of polymorphonuclears, production of pro-inflammatory cytokines, and associated acute lung injury (ALI).[10]

In COVID-19, there is a high interleukin-6 (IL-6) serum level with a reduction of NO level; therefore, PDE5 inhibitors like sildenafil may be used in the management of COVID-19 since they inhibit other types of coronavirus.[11]

Therefore, the aim of the present study was to review the possible role of PDE5 inhibitors in the management of COVID-19 patients.

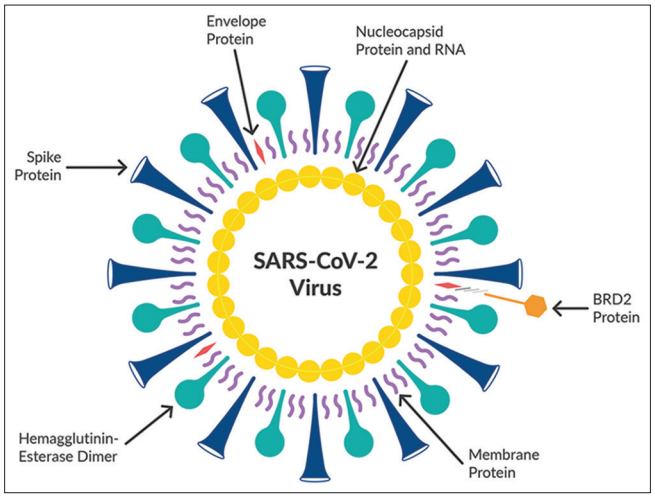

Figure 1: Genomic structure of severe acute respiratory syndrome coronavirus 2

Search Strategy

As a general rule, an endeavor of this study article was to present a minireview concerning the potential effect of PDE5Is. Evidence from experimental, preclinical, and clinical studies was appraised as minireview.

An array of search strategies was assumed that included electronic database searches of Scopus, Web of Science, Medline, Cochrane Central Register of Controlled Trials, and PubMed using MeSH terms, keywords, and title words during the search. The terms used for these searches were as follows: (PDE5Is OR sildenafil OR tadalafil) AND (Acute lung injury OR ARDS). (PDE5Is OR sildenafil OR tadalafil) AND (COVID-19 OR SARS-CoV-2). (PDEIs) AND (COVID-19 induced-cytokine storm). Reference lists of recognized and notorious articles were reviewed. In addition, all article types regardless of language were measured and case reports were also involved in this review. The key features of appropriate search studies were considered, and the conclusion was summarized in a minireview.

COVID-19 Acute Respiratory Distress Syndrome and Associated Acute Lung Injury

The pathological findings of COVID-19 significantly resemble those of SARS-CoV and MERS-CoV, Xu *et al*. illustrate that biopsy taken from the lung of COVID-19 patients is characterized by diffuse bilateral alveolar damage with abundant cellular fibromyxoid exudates, generation of the hyaline membrane, pneumocyte desquamation, and edema, indicating ARDS. In addition, lung interstitial inflammation with lymphocyte predominant and intra-alveolar viral cytopathic changes is observed.[12] However, Gattinoni *et al.* declare that COVID-19 pneumonia does not cause the typical feature of ARDS.[13]

The pathophysiology of ARDS in COVID-19 is due to host hyperimmune response, when SARS-CoV-2 binds pulmonary alveolar cells ACE2; it induces cellular damage and induction

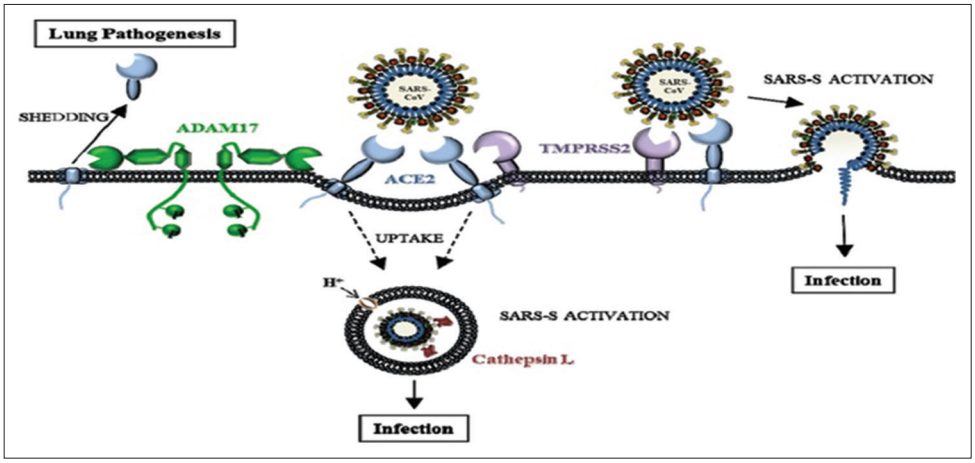

Figure 2: Pathogenesis of severe acute respiratory syndrome coronavirus 2

of the release of pro-inflammatory cytokines from dying pulmonary and immune cells [Figure 3].[14]

SARS-CoV-2 viral particles provoke host immune activation through activation of the complement cascade and alveolar macrophages which together forming a local immune complex. This immune complex participates in further stimulation of the complement system with augmentation of the systemic immune response through the massive release of pro-inflammatory cytokines including IL-6, IL-8, IL-1, and interferon-γ.[15]

Moreover, infiltrated neutrophils, lymphocytes, and resident macrophages lead to massive alveolar injury, vascular endothelial damage, microvascular thrombosis, and collateral tissue damage due to the release of pro-inflammatory mediators.[14] Indeed, in the end-stage ARDS, the progression of microvascular thrombosis and systemic inflammations lead to multiorgan injury [Figure 4].[16]

Wu and Yang reveal that SARS-CoV-2-induced ARDS is associated with cytokine storm mainly in patients with intensive care unit. The severity of symptoms in COVID-19 patients is correlated with the level of inflammatory and pro-inflammatory cytokines.[17] Moreover, IL-22 together with IL-17 and TNF-α provoke the release of endogenous antimicrobial peptide and upregulation of fibrinogen, mucins, serum amyloid protein, and lipopolysaccharide-binding protein that contribute in the progression of pulmonary edema. Thus, IL-17 is regarded as a potential biomarker in COVID-19, MERS-CoV, SARS-CoV, and pandemic HINI[18,19] However, Mehta *et al*. disclose that IL-6 is mainly linked with cytokine storm in COVID-19 patients, so IL-6 antagonist may be of great value in mitigation of cytokine syndrome in COVID-19 pneumonia.[20]

Cyclic Nucleotide Phosphodiesterase Enzyme Type 5 Inhibitors in COVID-19

PDE5Is such as sildenafil, tadalafil, and the nonselective inhibitor dipyridamole (DIP) are effective anti-inflammatory drugs and may have potential in the management of asthma and chronic obstructive pulmonary disease.[21] Of interest, prophylactic sildenafil therapy improves pulmonary cGMP levels, thereby reducing inflammation, capillary-alveolar protein leakage, alveolar fibrin deposition, and alveolar thickness in experimental ALI. This anti-inflammatory effect is mediated through inhibition of inflammatory cells mainly neutrophils and macrophages.[22] Besides, inhaled NO attenuates ALI through suppression of fibrin deposition and lung inflammation through NO-cGMP-dependent pathway thereby both NO and PDE5Is are interrelated in the mitigation of ALI.[23]

It has been shown that cGMP is involved in the downregulation of pro-inflammatory signaling and leukocyte recruitments in the tracheal smooth muscles. Interestingly, PDE5 was characterized in airway epithelium, airway smooth muscle, and in the media layer of the main pulmonary artery; furthermore, sildenafil induces a potent vasodilatory effect on the pulmonary artery.[24] Therefore, PDE5Is like sildenafil have significant anti-inflammatory effects and attenuation of pulmonary vasoconstrictions in ALI.[25] In ALI, apoptosis of pulmonary alveolar cells leads to dysfunction of endothelial/epithelial barrier through induction of immune reactions. Nevertheless, sildenafil inhibits apoptosis in neonatal rat with ALI through activation of the cGMP/NO pathway.[26]

Recently, Solaimanzadeh found a striking similarity between high altitude pulmonary edema (HAPE) and COVID-19 regarding pulmonary edema, hypoxia, hypocapnia, radiological pulmonary findings, PAH, high fibrinogen, and coagulopathy. Therefore, sildenafil may be of value in the reduction of COVID-19-induced PAH.[27] However, Luks *et al*. found that COVID-19-induced ARDS is a different entity from that of HAPE as COVID-19-induced ALI has proven to be a heterogeneous disorder and treated by antiviral agents and oxygen therapy unlike HAPE which respond to the oxygen therapy alone.[28]

It has been shown that inhalation of NO may be an effective agent in the management of COVID-19 patients as NO improves blood oxygenation in ARDS.[29]

Previously, in the SARS outbreak during 2002–2003, inhaled NO was useful therapy in the management of SARS-induced ARDS through the reduction of PHT and reduction of lung infiltrates.[30] Therefore, PDE5Is and NO donors improve pulmonary functions mainly ciliary movements and mucus production which together remove viral particles with noteworthy antiviral effect. Since pulmonary NO is downregulated during acute viral infections.[31] Herein, low pulmonary NO may facilitate the entry of SARS-CoV-2 and the development of COVID-19 pneumonia seeing as pulmonary disorders with low NO like cystic fibrosis is highly susceptible for recurrent viral pneumonia.[32]

On the other hand, Mergia and Stegbauer confirmed that PDE5Is reduce the activity of renin–angiotensin system (RAS) through inhibiting the secretion of renal renin.[33] RAS is involved in both acute kidney injuries (AKIs) and ALI in COVID-19-induced ARDS; therefore, AngII serum level is significantly augmented in COVID-19 patients. High AngII leads to AKI, ALI, and cardiovascular complications through impairment of NO production. Therefore, PDE5Is afforded a preventive task against AKI and ALI in the common complications of COVID-19 through the amelioration of AngII-induced endothelial dysfunctions.[34,35]

The binding of SARS-CoV-2 to ACE2 provokes innate immunity and coagulopathy leading to cytokine storm and hyperinflammation that collectively cause vasoconstrictions and microvascular injury with reduction of endothelial NO that is regarded as the link between AKI and ALI in COVID-19.[34] Besides, sildenafil reduces the expression and release of IL-6 and IL-8 in different inflammatory diseases; therefore, sildenafil may modulate cytokine storm in COVID-19 patients with ARDS.[36]

Dipyridamole (DIP), a nonspecific PDE5I, (inhibiting PDE2, PDE4, and PDE5)[8] with antiplatelet action has a role in the

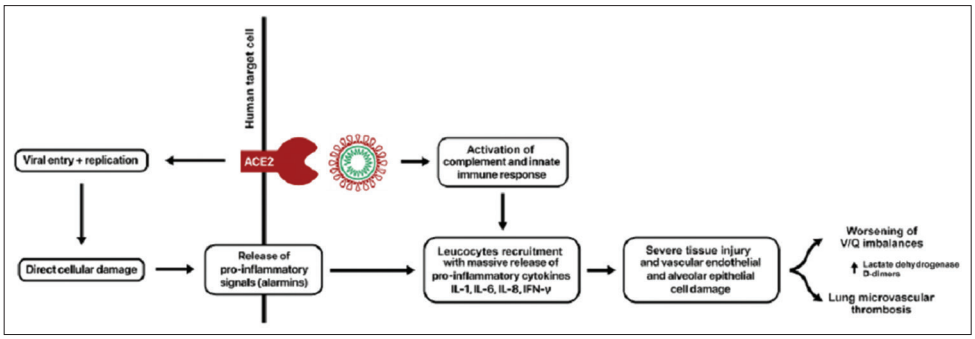

Figure 3: Pathophysiology of severe acute respiratory syndrome coronavirus 2 in acute respiratory distress syndrome[14]

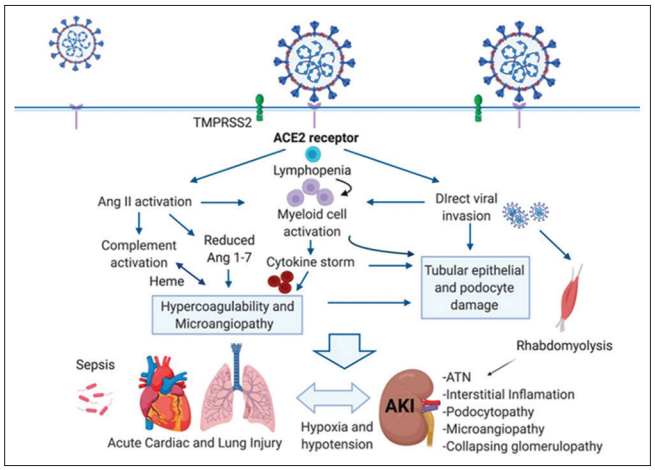

Figure 4: Systemic inflammations and multiorgan injury during severe acute respiratory syndrome coronavirus

management of COVID-19, as it has anti-inflammatory and antiviral action as well as mitigation of ALI. Besides, in silico study shows that DIP has significant anti-SARS-CoV-2 with marked improvement of COVID-19 outcomes.[37] DIP, in relationship with its PDE5I effect on platelets as well as its PDE4I effect on lymphocytes, prevents COVID-19-induced coagulopathy through modulation of platelet and lymphocyte counts as well as D-dimer production. Herein, DIP attenuates hypercoagulopathy-induced microvascular complications.[38]

It has been reported that SARS-CoV-2 is associated with diffuse alveolar hemorrhage (DAH), since viral replication is linked with platelet activations and formation of platelet-neutrophil aggregates with the generation of microthrombi. These hemostatic disorders provoke fibrinolysis, disseminated intravascular coagulopathy, and DAH. Therefore, the administration of antiplatelets like aspirin or DIP in the early phase of COVID-19 may reduce the severity of ARDS through the suppression of platelet-derived pro-inflammatory mediators.[39,40] Indeed, sildenafil possesses significant antiplatelet activity through platelet PDE5 and cGMP-dependent protein kinase.[41]

This study concluded that PDE5Is mainly sildenafil and the nonspecific PDE5I, DIP, have a noteworthy step in the management of COVID-19 patients with ARDS through mitigations of inflammatory changes and associated coagulopathy. Therefore, PDE5Is should be included and recommended in the basic therapeutic regimen of COVID-19 patients to prevent pulmonary and cardiovascular complications.

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Conflicts of interest

There are no conflicts of interest.

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