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Commentary

COVID-19 Severity Prevention: New Therapeutic Perspectives Based on Nitric Oxide Influences

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Abstract

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is still causing worldwide fatal cases of pneumonia (Coronavirus Disease-2019, COVID-19). While various types of vaccines have started to become available, the situation is worsened by viral mutations, which call into question the efficacy of anti-SARS-CoV-2 vaccines against new variants of the virus. The obtaining of medical drugs, complementary to vaccine procedures, thus remains essential. The time course of COVID-19 comprises two main consecutive stages: (1) at stage-1, the viral load and cytolysis are important. During this short phase, a deficit in the nitric oxide (NO) produced by the constitutive NO-synthases occurs in the lungs and allows the emergence of a pulmonary resistance that can be reduced by inhaled NO. (2) In stage-2, a pathologic cytokine storm takes place, together with the inducible NO-synthase (iNOS) expression, in various inflammatory and residential cells. In such conditions, the iNOS releases large amounts of pro-inflammatory NO that reacts with oxygen and superoxide radical to form deleterious NO-related free radicals. These radicals perpetuate acute systemic inflammation and compromise cellular integrity. In such a situation, the use of harmless iNOS inhibitors or of free-radical scavengers could be considered.

Keywords: SARS-CoV-2, COVID-19, cytokine storm, nitric oxide (NO), inducible NO-synthase (iNOS), antioxidants.

Introduction

At the end of 2019, the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was determined as responsible for grievous cases of Coronavirus Disease-2019 (COVID-19) pneumonia in Wuhan (China). Since then, the virus has spread to almost all countries. In many of these countries, infection continues to remain highly prevalent [1]. Immediately after the earliest medical alarms, worldwide scientific institutions have sought to produce a vaccine and various vaccines have become available [2,3]. Despite this, the pandemic becomes further worsened by the fact that the virus appears to be subject to mutations [4] and this ability led to question on the efficacy maintenance of anti-SARS-CoV-2 vaccines. Recent results suggest that the monoclonal antibodies in clinical use should be tested against newly arising variants, and that mRNA vaccines may need to be updated periodically to avoid potential loss of clinical efficacy [5]. To date, obtaining rapid-acting medical drugs, complementary to vaccination procedures, remains essential. For this purpose, a better understanding of the pathophysiological mechanisms of SARS-CoV-2 infection is necessary, especially in aged COVID-19 patients. To this end, we recently discussed the fact that SARS-CoV-2 is also a neurotropic virus entering the brain and capable of activating inducible nitric oxide synthase (iNOS) expression. Such biochemical activation conduces to an overproduction of nitric oxide (NO)-related free radicals that compromise neurocellular integrity and the sleep/wake cycle [6]. Here, focusing at the peripheral level (mainly the lungs), we further discuss how NO contributes to pathology during both steps of the disease. While a deficit in NO production by the constitutive NO-synthases takes place during the early phase (stage-1) of COVID-19 infection, during its second step (stage-2), a damaging high rate of iNOS-dependent NO production contributes to COVID-19 pathology. Specific iNOS inhibitors or antioxidants as vitamins C and E, and melatonin should be capable of reducing the stage-2 aggressiveness of the SARS-CoV-2 infection.

SARS-CoV-2 Infection Steps

Accumulating evidence now suggests that SARS-CoV-2 infects humans by binding to the angiotensin-converting enzyme 2 (ACE2) receptor [7]. The S-glycoprotein virion at the surface of SARS-CoV-2 attaches to the ACE2 receptor of human lung cells. After membrane fusion, the viral RNA genome released into the cytoplasm encodes nonstructural proteins [8]. At the onset of illness (first week post-infection: stage-1) the clinical progression of COVID-19 includes fever, cough and myalgia. Symptoms generally improve after a few days. Similar to SARS-CoV infection, the concomitant increase in SARS-CoV-2 viral load suggests that symptoms are mainly due to viral replication and cytolysis. During the subsequent phase of the illness (stage-2), patients may exhibit recurrent fever, diarrhea, oxygen desaturation and radiographic shadows in the lungs. After a ten-day period of uncontrolled viral replication with accompanying symptoms at the onset, a progressive decrease in viral shedding ensues [8,9]. Severity of clinical worsening depends on focal pulmonary complications (edema and inflammatory infiltrates) that occur after cessation of viral infection [9]. Such complications may result from an excessive host inflammatory response, comprising the induction of various interleukins (IL-6, IL-17A), tumor necrosis factor alpha, interferon gamma and NO free radicals [7,9].

SARS-CoV-2 Pathological Mechanisms Include a NO Component

To date, COVID-19 studies have focused on the "cytokine storm", while the complex role played by NO and metabolites remains poorly understood and largely ignored in the literature. NO is synthesized by NO-synthases (NOS) in the upper and lower parts of the respiratory system. Under healthy conditions, NO is produced by Ca^{2+}/calmodulin-dependent constitutive forms of NOS within the endothelial cells of pulmonary blood vessels (eNOS, endothelial NOS) or in airway nerve endings (nNOS, neuronal NOS) [10]. Nitric oxide is released in a picomolar range, playing a regulatory role for the maintenance of the pulmonary vasomotor tone [10]. During the early COVID-19 short stage-1, while the viral load pressure is highest, a deficit in NO production occurs, especially in the lungs. Such a negative variation in NO production induces an increase in pulmonary resistance that can be alleviated by inhaled NO [11]. The induction of a NO deficit after infection of a mammal by a pathogen has been previously documented through intraperitoneal injection of *Trypanosoma brucei brucei* in rats [12] or of *Plasmodium berghei* in mice [13]. In these experiments, decreased blood production of NO was observed during the early phase of the infection, coinciding with when the highest blood concentration of parasites was measured. The peripheral inhibition of the parasiticidal NO may be triggered by the parasite itself in order to deviate the NO metabolism to that of the arginase-dependent ornithine and polyamine derivatives [14]. Interestingly, in SARS-CoV-2 infected patients, a deficit in NO also seems to exist in the lungs during stage-1 of the disease, since NO inhaled at low concentrations reduces the pulmonary resistance and improves oxygenation in patients [11]. It is thus likely that when hosts are facing pathogens (including viruses), the concentration changes in NO occur with a similar modality in various animal species including humans, i.e., a decrease in the NO produced by the constitutive forms of the NOS. We stress that this situation may take place in the early COVID-19 stage-1 under the important pressure exerted by viral replication [12,13].

However, during the COVID-19 stage-2, in the conditions where the pathological cytokine storm takes place, the Ca^{2+}-independent iNOS is expressed by numerous inflammatory and residential cells including macrophages, fibroblasts, vascular muscle cells, epithelial cells, mast cells, neutrophils and chondrocytes [10]. It is known that, when exposed to endogenous cytokines and chemokines or to exogenous products (bacterial toxins, virus infection, environmental pollutants), the iNOS releases large amounts (nanomolar range or greater) of proinflammatory NO in the ensuing hours, or even days [10]. Under such circumstances, one may question whether NO, due to its ability to inhibit viral replication, could be responsible for the SARS-CoV-2-mediated decline in health observed in the second part of the disease [15]. NO reacts avidly with oxygen and superoxide radical to form NO derivatives including peroxynitrite ($ONOO^-$). The latter has a long half-life as a powerful oxidant that perpetuates acute systemic inflammation. In the pulmonary parenchyma, the damages induced will rapidly threaten patient life through the major injury of the alveolocapillary interface [16]. Other barriers such as those protecting the brain or kidney would undergo similar deleterious effects. In such a situation, the inhalation of NO, contrary to the early COVID-19 stage-1, may prove to be dangerous for infected patients.

Nitric Oxide Is Related to Frailty of Elderly Patients

Independently of infectious diseases, the iNOS enzyme is also permanently expressed throughout the aging process [17,18]. This age-dependent deterioration of the homeostatic mechanisms worsens the situation of COVID-19 patients by providing a supplemental iNOS-dependent fraction of NO in their lungs. In COVID-19, two independent enzymatic sources of NO are thus in action: (1) a constitutive NOS source that facilitates the oxygen transport through the modulation of the vascular tone; such a regulation is thought to be helpful, especially in COVID-19. (2) An iNOS source that releases greatly elevated amounts of NO, resulting in cell and tissue damage. To limit such deleterious effects, the administration of innocuous specific iNOS inhibitors and antioxidants (vitamins C and E, and melatonin) would be beneficial [6,17,18]. This strategy has proved successful in mouse hepatitis virus-induced demyelination [19]. Moreover, the use of vitamin C in COVID-19 patients was recently reported as capable of reducing inflammation and restoring a fraction of the inspired oxygen [20]. Very recently, interventions with bone marrow-derived stromal cells (bm-SC) were also proposed to combat the deleterious consequences of free radical production [21]. Further investigations remain necessary, however, before administration to humans.

Conclusion

During the COVID-19 stage-1, SARS-CoV-2 replication conduces to a reduction in the NO fraction produced by constitutive NOS. Such a decrease triggers immediately an increase in airway resistance, which can be alleviated by NO inhalation. During the COVID-19 stage-2, the marked cytokine-dependent inflammation contributes to the iNOS expression that leads to a deleterious overproduction of NO. Then, it must be emphasized that the inhalation of NO could be dangerous for COVID-19 patients. Moreover, in elderly patients, who host a permanent source of iNOS expression, the additive proinflammatory overproduction of NO aggravated by the cytokine storm might be fatal. Thus, during the extended time course of stage-2 COVID-19, the blocking of excessive NO production with specific inhibitors of iNOS should be considered.

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