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Prospects for the use of regulators of oxidative stress in the comprehensive treatment of the novel Coronavirus Disease 2019 (COVID-19) and its complications

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Abstract. – Some surface proteins of the newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can bind to the hemoglobin molecule of an erythrocyte, which leads to the destruction of the structure of the heme and the release of harmful iron ions to the bloodstream. The degradation of hemoglobin results in the impairment of oxygen-carrying capacity of the blood, and the accumulation of free iron enhances the production of reactive oxygen species. Both events can lead to the development of oxidative stress. In this case, oxidative damage to the lungs leads then to the injuries of all other tissues and organs. The use of uridine, which preserves the structure of pulmonary alveoli and the air–blood barrier of the lungs in the course of experimental severe hypoxia, and dihydroquercetin, an effective free radical scavenger, is promising for the treatment of COVID-19. These drugs can also be used for the recovery of the body after the severe disease.

Key Words:
COVID-19, Hemoglobin, Free iron, Oxidative stress, Uridine, Mitochondrial ATP-dependent potassium channel, ROS, Antioxidant, Dihydroquercetin.

Abbreviations

mitoKATP: mitochondrial ATP-dependent potassium channel; UDP: uridine-5'-diphosphate; UTP: uridine-5'-triphosphate; 5-HD: 5-hydroxydecanoate; ROS: reactive oxygen species.

Introduction

The current coronavirus disease 2019 (COVID-19) caused by a newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is considered to be a serious infectious disease due to the extreme virulence of the virus, uncommon course, and severe complications[1,2]. COVID-19 is an unusual respiratory infection, because the coronavirus attacks hemoglobin (Hb) molecules in the blood[3]. Clinical studies of almost 100 patients from Wuhan revealed that the level of Hb in the blood of most people infected with SARS-CoV-2 decreased significantly[4]. Therefore, the oxygen-carrying capacity of red blood cells can be compromised by SARS-CoV-2, which, in turn, may lead to severe hypoxemia and oxygen deficiency in many organs[2,4].

The data from Chinese scientists indicate that surface membrane proteins of SARS-CoV-2 (the surface glycoproteins) can bind to the 1-beta chain of the Hb molecule of red blood cells, which leads to the displacement of the iron ion from the heme[3]. Free iron ions released from the hemes can enter the bloodstream and spread through the tissues. To bind harmful iron ions, large amounts of the major iron storage protein ferritin are produced as part of a normal physiological response to iron overload[4,5]. This is why serum ferritin is considered as a biochemical marker for COVID-19[6].

In the absence of an iron ion, the affected Hb can no longer bind to oxygen and carbon dioxide; that is, it cannot fulfill its function[3]. It becomes useless and is simply transported by the blood along with the viruses attached to its porphyrin, without delivering oxygen to tissues. This can eventually lead to the development of hypoxia, followed by tissue damage. A number of studies have shown that the body can compensate for this oxygen deficiency in tissues by forcing the kidney cells to secrete hormones such as erythropoietin, which promotes the production of new red blood

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cells by the bone marrow[7]. In this case, the use of erythropoietin does not eliminate the root cause of the disease; the newly formed erythrocytes may also be further attacked by SARS-CoV-2[7].

As known, each subunit of the Hb molecule has a heme group with a divalent iron ion which, in its free form, is quite toxic[8]. In the Hb molecule, it is locked in the center of the special protein porphyrin, acting as a "container". Thus, the iron ion is safely transported by Hb to tissues[8]. When the iron is divalent, Hb can bind the oxygen molecule in alveolar cells, and the iron is oxidized to a trivalent form. When Hb is made available to other cells in the body, it can release oxygen atoms and capture carbon dioxide, and iron is reduced to a divalent[9].

The bioinformatics analysis revealed that the ORF8 protein and the surface glycoprotein of SARS-CoV-2 can bind to porphyrin[3], while the toxic iron is released and transferred throughout the body[5]. In the blood and tissues, free iron is known to be easily oxidized and trigger the peroxidation of lipids and proteins[10]. The binding of iron ions with ferritin can reduce the oxidative damage to tissues. This is probably the reason why COVID-19 is characterized by a significant increase in the level of serum ferritin[3-6], which can be a compensatory mechanism that reduces the labile iron pool in the organism[11].

Free iron is highly reactive and can catalyze the generation of damaging reactive oxygen species (ROS) via the Fenton and Haber-Weiss reactions[10]. The enhanced level of ROS due to iron overload can cause damage to biomolecules such as lipids, proteins, and nucleic acids, leading to tissue degradation in various pathologies, including viral infections[12,13]. Under normal physiological conditions, iron metabolism is tightly controlled to protect the cell against toxicity[14]. Several protection mechanisms exist to maintain the redox balance in the body. In particular, the iron homeostasis in the lungs is maintained by three main protective mechanisms, two of which are in the pulmonary alveolus[14]. The first is macrophages, nonspecific killer cells, which can detect and eliminate reactive free radicals. The second mechanism is the alveolar epithelium, which is a target of COVID-19. Alveolar epithelial cells contain a great quantity of antioxidant molecules sufficient to neutralize ROS under normal physiological conditions. In the case of COVID-19, when the amount of free iron and ROS production dramatically increase, natural antioxidants present in the lung tissue can be insufficient to prevent oxidative stress. This can lead to severe complications and bilateral pneumonia, which is not typical of a common infectious disease[1]. The data of radiography and computed tomography have shown that novel coronavirus-induced pneumonia is accompanied by massive oxidative damage to the lungs and other tissues[1,2,4], which may indicate a chemical rather than viral etiology. This has also been confirmed by diagnosticians and pathologists who, based on the observation of severely affected patients with COVID-19, call this disease not pneumonia but hypoxic damage accompanied by multiple organ failure due to the lack of oxygen supply to all tissues[15,16].

The data accumulated during the autopsy of deceased COVID-19 patients show that not only the lung is affected by this disease. Other organs also suffer from the lack of oxygen in the absence of functionally active Hb of erythrocytes in the blood and from elevated ROS production[15,16]. The liver, for example, plays a key protective role by removing potentially toxic free iron from the circulation and storing it in "iron storage" in hepatocytes, which can eventually become overloaded. The impairment of the liver function and damage to hepatocytes is accompanied by the release of the hepatic enzyme, alanine aminotransferase, in the blood, which is also a marker enzyme in COVID-19[2]. A moderate increase in the serum alanine aminotransferase level along with a compensatory increase in Hb at the early stage of COVID-19 is associated with a poor prognosis. This indicates a high probability of subsequent development of the severe acute respiratory distress syndrome in patients infected with SARS-CoV-2[2].

Subsequently, the development of oxidative stress can serve as a key pathogenic factor in damage to the brain and nervous tissues[16]. In the end, if the immune and antioxidant defense systems are not efficient in clearing the virus, and the oxygen saturation of the blood becomes too low, all organs of the body gradually begin to shut down[1]. In this case, the transfusion of red blood cells with redox-active hemoglobin can help[1] or, as we suggest, artificial blood substitutes may be used.

In addition, there are several new approaches to the treatment of COVID-19. One approach involves the selection of drugs that inhibit the replication of the coronavirus, resulting in its inability for reproduction[17]. Another approach is to protect the Hb molecule from destruction for which antimalarial drugs such as hydroxychloroquine

and chloroquine can be used[18-21]. However, the therapeutic effect of these drugs on COVID-19 has not yet been clinically proven. The difficulty in the use of antimalarial drugs is that they have rare but potentially deadly side-effects[22]. In addition, their dosage in the case of COVID-19 needs to be amped up in comparison to malaria, which can sometimes cause persistent arrhythmias[18,22]. Recent studies have also suggested the use of the anti-influenza drug favipiravir, which selectively and potently inhibits the RNA-dependent RNA polymerase of RNA viruses. Favipiravir was discovered through screening the chemical library for anti-viral activity against the influenza virus[3,23].

As mentioned above, Hb affected by SARS-CoV-2 is permanently deprived of the ability to transport oxygen and carbon dioxide, which may ultimately trigger the development of hypoxia in many organs, in particular, the lungs and the brain. Moreover, experimental data indicated that SARS-CoV induces enhanced ROS production in cell cultures, which is likely to be responsible for the virus-induced apoptotic cell death[24,25]. This prompts us to suggest the use of uridine, an antihypoxic drug, as a part of the complex therapy of COVID-19. An analysis of the mechanisms mediating the effects of uridine and its derivatives (UTP and UDP) on cellular metabolism is presented in the figure.

Recently, we have revealed a protective effect of uridine on the ultrastructure of rat lung tissue exposed to acute normobaric hypoxia[26]. An animal was placed for 30 min in a pressure chamber, which, instead of 21% oxygen, contained a gas mixture of 7% oxygen and 14% inert gaseous nitrogen. It should be noted that the lungs were predominantly affected by hypoxia while, in the heart, pathological changes in the ultrastructure of cardiomyocytes were less pronounced[26-28]. Severe hypoxia led to pulmonary edema and a sharp increase in the thickness of the air–hematological lung barrier (ABB), and pathological changes were observed in all its layers[26]. The thickness of the epithelial layer of the ABB increased by 61%, that of the interstitial layer by 47%, and that of the endothelial layer increased 2.3 times. Thus, hypoxia resulted in the interalveolar edema of all the layers, which was well defined in electron microscopy images. Uridine was shown to have a marked positive effect against hypoxic damage to the lungs. It protected the ABB from the hypoxia-induced hyperhydration; the thickness of its epithelial and endothelial layers became similar to that in control. After treatment, only the interstitial layer of the ABB did not completely recover[26].

Acute and severe hypoxia also affected the ultrastructure of mitochondria in lung cells[26]. The following structural alterations of lung mitochondria were observed: the swelling of the mitochondrial matrix to different degrees, partial or complete vacuolization, disorders in crista arrangement, and destruction of mitochondrial membranes, mainly of the inner and sometimes of the outer ones. It should be noted that, under conditions of hypoxia, some adaptive changes in pulmonary alveoli were found. The mechanism of adaptation of lung cells to hypoxia can be related to an increase in the morphogenesis of mitochondria, since their total number increased. The administration of uridine to animals reduced the number of mitochondria with impaired ultrastructure and prevented the hypoxia-induced swelling of the organelles. The protective effect of uridine on ultrastructural changes in the pulmonary alveoli and mitochondria can be associated with the formation of uridine-5'-diphosphate (UDP), a metabolic activator of the mitochondrial ATP-dependent potassium channel (mitoK_{ATP}). The administration of the selective inhibitor of the channel 5-hydroxydecanoate (5-HD) before the injection of uridine eliminated almost all the positive effects of uridine[26]. According to the literature and our data, the mitoK_{ATP} is involved in the protection of tissues from hypoxic stress and the development of urgent adaptation to oxygen deficiency[28-31]. It was found that the activation of the mitoK_{ATP} prevents the formation of increased amounts of ROS, which can oxidize DNA, proteins, and lipids, thereby altering their structure, activity, and physical properties[31,32].

It should be emphasized that the positive effect of uridine is mainly related to the fact that when it enters the cell, it can then be converted into UDP, which, as we have shown, can act as an opener of the mitoK_{ATP}[33]. UDP itself does not penetrate the plasma membrane under physiological conditions[34,35], but it can be synthesized in cells from exogenous uridine[36]. The concentration of uridine in blood plasma and tissues is regulated by cellular transport mechanisms and the activity of uridine phosphorylase that is responsible for the reversible phosphorolysis of uridine to uracil[34]. The expression of uridine phosphorylase is directly regulated by the tumor suppressor gene *p53*[34]. The intravenous injection of uridine leads to an increase in its level in the blood serum, and

within 0.5-1 h after the synthesis of UDP and UTP in the cell, the manifestation of therapeutic effects can be observed[36-38].

We have demonstrated earlier that uridine, a metabolic precursor of the mitoK$_{ATP}$ activator, UDP, prevented the excessive production of hydrogen peroxides and diene conjugates in the heart tissue on an animal model of acute myocardial ischemia[37,38]. Simultaneously, uridine limited changes in oxidative and energy metabolisms in the heart. It decreased the size of the necrosis zone in the myocardium and prevented disturbances in the synthesis of glycogen, ATP, and creatine phosphate, which preserve the myocardial function during hypoxia[37,39]. The stimulatory effect of uridine on glycogen synthesis can also alleviate pathological changes in diabetes mellitus[40], which causes increased complications in COVID-19[2].

Pyrimidine nucleoside uridine, which is necessary for the synthesis of RNA and biomembranes, is a key element in the regulation of normal physiological processes occurring in the cell[39] and a number of pathological conditions[40,41]. The biological effect of uridine is associated with its metabolism (Figure 1). When intracellular uridine is converted into UTP, and then into CTP (there is no transport system for cytisine), it can affect the synthesis of brain lipids and restore the membrane structure, in particular, the myelin sheath on the axon of neurons. Therefore, uridine has long been used to restore the memory function and treat neurodegenerative disorders[42]. However, uridine phosphonucleotides, unlike uridine, do not enter the cell[34,43]. Recently, we have shown

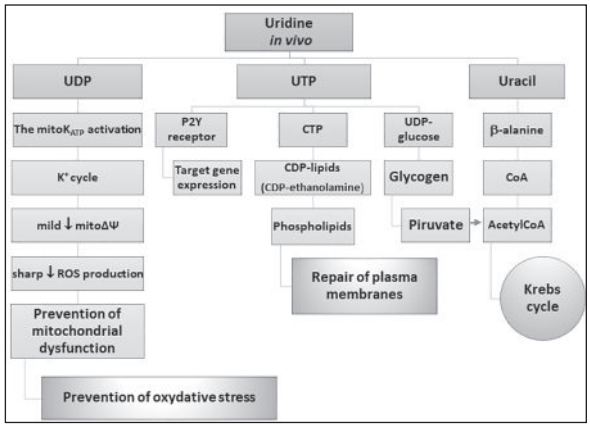

Figure 1. The pathways that mediate the protective effect of uridine *in vivo* against the development of oxidative stress and energy imbalance.

that uridine has an antihypoxic effect, which positively affects the function of the nervous[29], cardiovascular[37,38], and respiratory[26] systems, as well as exhibits anti-inflammatory activity[36]. We suggested that these effects of uridine could be associated with its conversion into UDP in the cell[33,36].

It is well known that the specific cells of the immune system of a virus-infected organism begin to secrete various pro- and anti-inflammatory cytokines, including interleukin (IL)-10, IL-6, IL-17, IL-23, interferon (IFN)-α, IFN-γ, BAFF, and others. Abnormal release of diverse cytokines can end with the development of a "cytokine storm", which plays a crucial pathogenic role in infectious diseases, including COVID-19[1,2,4,44]. Under normal physiological conditions, cytokines and ROS are signaling molecules and can modulate key transcription factors, which in turn regulate the synthesis of proteins necessary to protect against a stressful factor. The production of cytokines by immune cells in the appropriate amounts protects the body from viruses and bacteria. However, an excess of cytokines produced during a cytokine storm induces an overactive immune response, which can cause damage to many organs, especially the lungs[2]. As follows from our studies, uridine can eliminate the cytokine storm[36].

The anti-inflammatory effect of uridine is manifested in the inhibition of excessive secretion of tumor necrosis factor-α, IFN-γ, IL-1, IL-2, and IL-6 pro-inflammatory cytokines, observed during the development of inflammation[36]. The mechanisms mediating the effects of uridine are regulated by the activation of glycogen synthesis and opening of the mitoK$_{ATP}$, which increase the energy potential of the cell and reduce oxidative stress[36]. The current reports show that patients with severe COVID-19 present a cytokine storm syndrome characterized by different cytokine profiles[1]. In excess, these cytokines can damage the walls of blood vessels and cause hemorrhages in the brain, which results in the development of certain neurological symptoms[1,2,4]. Our studies show that uridine can normalize the imbalance of immune responses and decrease the activity of the nuclear factor (NF)-κB signaling pathway[36], and therefore be a promising drug for the treatment of COVID-19.

It should be noted that a diet enriched with antioxidants also reduces the cytokine storm[45], and therefore, may also be a promising approach to the treatment of the disease. Furthermore, it

has become clear that older people are at a significantly increased risk for developing severe complications from COVID-19[4] not only because they have many concomitant diseases but also because their oxidative metabolism is impaired. As is known, aging is associated with an increase in ROS production in tissues[31,37]. We also do not exclude that this may be also associated with an aging-related decrease in the activity of the mitoK_{ATP} channel[37], which leads to increased generation of ROS by mitochondria[30,32]. Therefore, the use of antioxidant medications may be recommended to maintain the intracellular redox balance and reduce oxidative stress for older people with COVID-19.

Considering possible development of the cytokine storm, hypoxemia, and oxidative damage to tissues during COVID-19, which was also confirmed by clinical studies[2,4], we suggest that effective antioxidants are useful for the prophylaxis of hyper-inflammation and the suppurative treatment of the disease. The supplementation of antioxidants may also help to accelerate the recovery of the body after COVID-19. An effective scavenger of free radicals is dihydroquercetin.

The water-soluble dihydroquercetin "Taxifolin aqua," developed by Advanced Technologies Ltd (Russia) has been registered as a biologically active additive and has a certificate of state registration no. RU.77.99.11.003.E.003036.07.18. The drug has a powerful antioxidant effect, which is several times higher than that of the well-known natural analog vitamin C[44]. Aqua dihydroquercetin can protect and strengthen blood vessel walls, reduce their permeability and fragility, restore blood microcirculation, and normalize metabolism in cells[46]. It should be emphasized that high-dose vitamin C is now recommended for the treatment of COVID-19[47,48].

It was found that, in patients with acute pneumonia who received complex therapy in combination with dihydroquercetin, the signs of pulmonary inflammation and the level of ROS production in the blood serum disappeared faster compared to those who did not take it[49]. The use of dihydroquercetin as a part of the integrated therapy strategy allows one to normalize the blood circulation in the mucous membrane of the bronchi in a short time, thereby contributing to the rapid elimination of local inflammation[49,50].

It was also observed that, in patients with chronic obstructive pulmonary disease who have abnormalities in the endobronchial microcirculation of the bronchial mucosa, dihydroquercetin decreased or removed, depending on the severity of the disease, characteristic morphofunctional disorders in the microvascular bed[51].

Conclusions

Considering the literature data and the experience of practicing doctors, one can assume that the COVID-19 infection is accompanied, particularly in severe cases, by pulmonary oxidative stress, which causes profound structural changes in the lung tissue. Due to the coronavirus-induced degradation of Hb molecules, a decrease in the pool of redox-active erythrocytes and the accumulation of a large amount of free iron ions occur; in all organs and tissues, hypoxia and oxidative stress may develop. To prevent these events in COVID-19 patients, we propose to use the pyrimidine nucleoside uridine and the water-soluble antioxidant dihydroquercetin, which are promising in the treatment of hypoxia-induced injury of the lungs and respiratory diseases. They may be useful for the treatment of COVID-19 patients and the restoration of their body after such a serious illness.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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