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Pathogenesis of Neurological and Mental Disorders in Patients with Covid-19: Possible Role of Reactive Nitrogen and Oxygen Species

Reutov VP[1*], Sorokina E G[2], Samosudova N V[3], Okhotin V E[4]

[1]*Institute of Higher Nervous Activity and Neurophysiology of the Russian Academy of Sciences, Moscow. Russian Federation*

[2]*National Medical Research Center for Children's Health, Moscow, Russia Moscow, 119991 Russia*

[3]*Kharkevich Institute of Information Transmission Problems, Russian Academy of Sciences, Moscow, 127051 Russia*

[4]*Pacific State Medical University, Vladivostok, 690950 Russia*

[*]Corresponding author

Reutov VP, Institute of Higher Nervous Activity and Neurophysiology of the Russian Academy of Sciences, Russian Federation; Moscow, 117485 Russia. valentinreutov@mail.ru

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Abstract

The pathogenesis of neuronal and mental disorders are analyzed according to the literature and compared with other neuronal damage during hypoxia/ischemia, inflammatory processes, and immune/autoimmune diseases. The free radical component of the development of the pathogenesis of COVID-19 is analyzed, which is activated at all stages of the disease, starting with the first manifestations of inflammatory reactions, during the development of a «cytokine storm», hypoxia/ischemia, as well as activation of immune/autoimmune reactions and processes. These free radical components are realized against the background of disruption of the cycles of nitric oxide and superoxide anion radical, and, leads to the formation of extremely high concentrations of very active radicals of nitrogen dioxide (NO_2), OH-radicals, peroxynitrites. As a result of these processes, nonspecific reactions are activated that are characteristic of the development of any typical pathological process, which is a common component of almost all known pathological processes. It is suggested that the similarity of structural and ultrastructural changes in neurons and glial cells of the brain during hypoxia/ischemia, glutamate neurotoxicity, traumatic brain injury have similarities with those changes that are characteristic of all stages of COVID-19 development and are due to the activation of oxidative and nitrosative stress and increased formation of highly reactive nitrogen species (RNS) and reactive oxygen species (ROS) capable of damaging almost all molecular, biochemical and chemical components of cells.

Keywords: COVID-19, Neuronal and Mental Disorders, Oxidative and Nitrosative Stress, Hypoxia/Ischemia, Inflammatory Processes, Immune/Autoimmune Diseases, Nitric Oxide, Nitric Dioxide, Nitric Oxide Cycle, Superoxide Anion Radical Cycle

It is not life in improper conditions or a distortion alone that causes disease; in contrast, disease starts with a failure of the regulatory system.
R. Virchow (1821–1902)

We often ignore the fact that all processes are cyclic: every physiological process has its cycle.
L.A. Orbeli (1882–1958)

Starting a new period of life on Earth after the Covid-19 Pandemic

The number of Covid-19 mutations at the end of August, when we submitted the article to print,was known to be 8. However, they wrote that there are much more of them. Over the past 10 days, 22 more variants of the Coronavirus have become known. Therefore, we can say that the population of the Earth has entered a new period in the development of life on our planet. It is not known only how this period will end and how many people will remain on our planet.

Introduction

The new 2019 coronavirus infection COVID-19 poses a serious threat to humanity. In December 2019, an epidemic of coronavirus infection broke out in Wuhan, China. Li Wenliang (Chinese: Li Wenliang; 12 October 1986 – 6/7 February 2020), a Chinese ophthalmologist at Wuhan Central Hospital, was the first to raise the alarm about a new coronavirus similar to SARS (Figure.1). Li Wenliang died at the age of 34. On January 30, 2020, the World Health Organization (WHO) announced the SARS-CoV-2 outbreak as a public health emergency of international concern [1]. On February 11, 2020, WHO officially designated the infection with the new coronavirus as Coronavirus disease 2019: COVID-19 [1]. Most people infected with the COVID-19 virus experience mild to moderate respiratory illness and recover without specific treatment [2]. People with underlying medical conditions such as diabetes, cardiovascular disease,

cancer, and chronic respiratory diseases are more likely to develop serious illnesses and complications [1, 2]. Given the high inflammatory component in the pathogenesis of COVID-19, and based on early clinical reports, significant cardiovascular complications can be expected in patients with severe COVID-19 infection. [3-5].

Figure 1: ***Li Wenliang before (a) and after infection (b) (Chinese 12 October 1986 – 6/7 February 2020), a doctor at Wuhan Central Hospital, died at the age of 34.***

Li Wenliang, a Chinese ophthalmologist, was the first to raise the alarm about a new coronavirus similar to SARS. On February 11, 2020, WHO officially designated the infection with the new coronavirus as Coronavirus disease 2019: COVID-19 [1].

Neurological disorders occur in approximately 35–40% patients with COVID-19. All neurological disorders can be divided into 3 types: 1) manifestations of the central nervous system (dizziness, headache, impaired consciousness, ataxia, convulsions); 2) manifestations from the peripheral nervous system (violation of taste, smell, vision, neuralgia); 3) damage to the musculoskeletal system and impairment to control one's body in patients with COVID-19 [6-8].

In the work Lin Mao et al. were the first to analyze neurological manifestations in hospitalized patients with COVID-19 in Wuhan, China [7]. In this study, 78 (36.4%) of 214 COVID-19 patients had neurological manifestations affecting the central and peripheral nervous system and skeletal muscle. In most cases, these neurological symptoms were seen early in the disease, before the typical symptoms of COVID-19 developed. Patients with severe COVID-19 infection were more likely to have cerebral symptoms and signs of nervous system damage, such as ischemic/hemorrhagic strokes and encephalitis [7-11]. They were more likely to have lymphocytopenia, leukocytosis with neutrophilia, increased levels of C-reactive protein, D-dimers, signs of liver and kidney damage (increased levels of lactate dehydrogenase, alanine and aspartate aminotransferases, creatinine, residual nitrogen, urea), compared with patients with lighter the course of the infection [7].

In another work, Neo Poyiadji et al (2020) described a case of acute hemorrhagic necrotizing encephalopathy with symmetrical multifocal lesions, mainly in the thalamus and other foci in the brain stem, white matter of the cerebral hemispheres, and cerebellum [9]. Acute hemorrhagic necrotizing encephalopathy is a rare complication of influenza and other viral infections and is associated with a cytokine storm that disrupts the blood-brain barrier (BBB). Such complications are mainly described in pediatric practice, but it is known that acute hemorrhagic necrotizing encephalopathy occurs in adults [9]. Despite numerous publications on the neurological pathology in COVID-19, risk factors, pathogenesis and relations between neurological disorders and coronavirus infection remain unclear. This problem is exacerbated by the fact that the coronavirus mutates.

Cerebrovascular pathology in 221 patients, described by Y. Li et al., occurred in 5.9 % of cases – the majority was comprised by ischemic stroke, and as a whole it was associated with a more severe disease course [10]. T. Oxley et al. described 5 patients (less than 50 years of age) with a large-vessel stroke occuring as a result of COVID-19 [11]. It has been shown that meingoencephalities may be linked to COVID-19. Apart from that, it is well established that COVID-19 may lead to deterioration of concurrent somatic and neurological diseases, worsening the prognosis [9-12].

Mutations of the Coronavirus COVID-19

Currently, the World Health Organization (WHO) includes 8 coronavirus variants / mutations in the main list of COVID-19 (VOC – Variants of Concern) strains. These variants received the names of the strain's "alpha" (Great Britain), "beta" (South Africa), "gamma" (Brazil), "delta" (India). Relatively recently, the list of options that arouse interest and concern of virologists was replenished with the strain's "eta" (first registered in the UK and Nigeria), "kappa" (India) and "lambda" (Peru), and finally, in November 2020, the strain was described «Iota» (first registered in the USA). With each new strain, the ability of COVID-19 to kill a person change [10-22]. Some scientists believe that this ability only increases with each new strain [23-28].

After August 12, 2021, it became clear that COVID-19 has not gone anywhere and, most likely, will never leave us. Many countries are now experiencing the third wave of this disease. Japanese doctors believe that the fifth wave of COVID-19 has begun in Tokyo after the 2020 Olympics. More than 6 months ago (February 4, 2021), new information appeared that the achievement of herd immunity is impossible in the conditions of circulation in the human population of such strains as, for example, the strain "delta" (India). This data came from Andrew Pollard, the team leader for the Oxford COVID-19 vaccine (Figure. 2), and was published in The Guardian, the UK's most widely read daily left-wing liberal newspaper [23].

Figure 2: ***Sir Andrew John Pollard (born 1965), British immunologist, Professor of Paediatric Infection and Immunity, the team leader for the Oxford COVID-19 vaccine [23]***

He warned the world for the first time that herd immunity would not occur after vaccination against COVID-19, at least during 2021.

Life of the WHO Chief Scientist on a «razor's edge».

Now, notes The Guardian, about 75% of the UK adult population has received two doses of the coronavirus vaccine. Since all the vaccines taken together have not yet stopped the spread of COVID-19, this may mean that reaching the herd immunity threshold is not possible, at least in the near future. However, until recently, it was believed that the only way to achieve herd immunity on a global scale was vaccination. However, herd immunity will definitely not emerge this year, according to WHO Chief Scientist Sumiya Swaminathan (Figure. 3) [24]. However, even if herd immunity develops in several countries, «it will not protect people around the world». This is the worst news we have heard about COVID-19 over the past 6 months.

Figure 3: ***Soumya Swaminathan Yadav (born 1959) is an Indian paediatrician and clinical scientist.***

Starting from school, she brilliantly performed throughout her life everything that she did herself or she was instructed to do. Dr. Swaminathan is currently the Chief Scientist (2019) at WHO. However, the Indian Bar Association (IBA), led by attorney Deepali Oja, filed a lawsuit against WHO Chief Scientist Dr. Sumyu Swaminathan on 25 May 2021, accusing her in a 71-point summary of causing the death of Indian citizens by introducing them misleading the relatively cheap and effective antiparasitic drug IVERMENTIN (IVE). However, there is still not a single drug developed specifically for COVID-19. Malaria medicines, despite the side effects, have been used in various countries around the world, including India, China, the United States and Russia. If the WHO Chief Scientist Dr. Sumya Swaminathan is found guilty in a trial in India, the WHO scientist could be sentenced to death or life in prison. Attorney Deepali Oja, a leading attorney for the Indian Bar Association, threatened to hold Dr. Swaminathan accountable for "every death" caused by her actions or omissions. Thus, Dr. Swaminathan is accused of misconduct, as she – the Chief Scientist of WHO – used her position to lobby the special interests of pharmacological campaigns producing vaccines against COVID-19 [24].

Pathogenesis of Neurological and Mental Disorders Associated with Covid-19 Infection

Currently, the literature discusses issues related to the direct effect of coronavirus on the nervous system; the probability of its penetration through the olfactory and trigeminal nerves and by the hematogenous route through the endothelial cells of the blood-brain barrier (BBB) is analyzed [19, 25, 26]. Immunopathogenesis of disorders of the nervous system in the acute stage of the disease can be caused by an excessive immune response – «cytokine storm» and increased permeability of the blood-brain barrier (BBB) [10-19, 25, 26, 29].

«Cytokine storm» is the main danger of the «first wave» of COVID-19 infection.

«Cytokine storm» is an extremely severe systemic inflammatory reaction. The second name of the cytokine storm is hypercytokinemia, since the condition is accompanied by excessive activation of immunocompetent cells and uncontrolled production of inflammatory cytokines. Cytokines are peptide molecules, the appearance of which indicates that the body is in danger. They play the role of a stimulator of immune responses to eliminate infectious pathogens. Lymphocytes are the main producers of cytokines. When the mechanism of active production of these peptides is triggered, all signs of inflammation appear. Doctors call this condition «the body's suicide». The cytokine storm is one of the main reasons for the death of patients with COVID-19, when the body's immune cells cease to distinguish between their own and foreign proteins, storming everything. In this case, healthy organs come under attack – the brain, heart, liver, kidneys. Multiple organ failure begins. However, doctors still do not always understand the danger that develops as a result of the activation of free radical processes, oxidative and nitrosative stress, and an increase in the concentration of reactive nitrogen and oxygen species during a cytokine storm. This uncontrolled surge of immune cells, and associated molecules and macromolecules, often leads to fatal organ shutdown. However, doctors still do not always understand the danger that develops as a result of the activation of free radical processes, oxidative and nitrosative stress, and an increase in the concentration of reactive nitrogen and oxygen forms during a cytokine storm. Particularly dangerous are highly reactive molecules of nitrogen dioxide (NO_2), OH-radicals, peroxynitrites, which again decompose into NO_2 and OH-radicals and support the course of self-destructive reactions of the body, developing with the participation of positive feedbacks. All these pathological processes are accompanied by disruption of normal cyclic regulatory processes and lead to the death of the organism. Cycles of nitric oxide and superoxide anion radical, which we will discuss below, play an important role in maintaining the concentration of reactive nitrogen and oxygen species. Is it possible to catch the «first wave» and prevent further catastrophe?

A blood test can show elevated levels of markers such as interleukin-6, interleukin-1, C-reactive protein, and tumor necrosis factor-alpha. The sooner doctors identify a cytokine storm and begin treating it, the more likely the patient will survive. How should a polyclinic doctor react when he sees an elevated C-reactive protein in the patient's tests? The answer is simple – he should immediately call an ambulance and send the patient to a specialized department for differential diagnosis of COVID-19. Nothing can be done about the «cytokine storm» in the outpatient department [25-28].

The Indirect Effect of The Virus, Complications of The Disease

Such as encephalopathy, myopathy, neuropathy of critical conditions can be caused by hypoxia/ischemia; respiratory and metabolic acidosis; energy deficit; associated with edema and mitochondrial damage; by disregulation of ionic homeostasis; further edema of cells of various organs; autoimmune inflammatory and demyelinating processes; the development of organ failure [5-22, 25-28].

COVID-19 can damage the blood-brain barrier (BBB) through the vascular system (capillary endothelium) [19]. It is assumed that in addition to damage to the central nervous system (CNS) through angion-converting enzyme-2 receptors (ACE-2 receptors), coronavirus can induce direct damage of neurons in the cardiorespiratory centers of the brain stem. A

genetic predisposition to an increased risk of neurological complications associated with SARS-CoV-2, in part due to ACE-2 polymorphism, is considered [19, 26]. Angiotensin-converting enzyme (EC 3.4.15.1) is a central component of the rennin-angiotensin system (RAS), which controls blood pressure by regulating the volume of fluids in the body. It converts the hormone angiotensin-I to the active vasoconstrictor angiotensin II. To enter the cell, SARS-CoV-2, like other coronaviruses, uses a spike (S-protein) protein. With this, it attaches to a target on the surface of the host cell. Genome sequencing of the new coronavirus showed that in his case, the target is angiotensin-converting enzyme 2 (ACE2). The SARS-CoV virus, one of the closest relatives of the new coronavirus, also binds to the same molecule [29]. Research of the immunopathogenesis of COVID-19 has shown that increased absorption of coronavirus by macrophages can lead to activation of macrophages, secretion of cytokines and other chemokines, as coronavirus-specific T cells and antibodies activate macrophages, which leads to their migration to the central nervous system (CNS) and, ultimately, to demyelination – selective damage to the myelin sheath passing around the nerve fibers of the central nervous system and the peripheral nervous system [26-31].

Morphological studies: similarity of structural and ultrastructural changes in brain neurons during hypoxia / ischemia, glutamate neurotoxicity, traumatic brain injury and exposure to various strains of COVID-19

Based on the results of more than 2,000 autopsies of deaths from COVID-19, Moscow pathologists compiled an atlas of pathological changes identified at different stages of this disease [32]. The Atlas allows you to see the spectrum of possible manifestations and complications of COVID-19, outline ways to study the pathogenesis and morphogenesis of the identified structural changes, improve methods of diagnosing and treating patients, and make a detailed classification of causes of death directly or indirectly related to COVID-19 [32]. The characteristic morphological signs of the brain in COVID-19 were the following changes: pia mater plethora; varying degrees of cerebral edema; hemorrhage in the pia mater; destructive-productive throm bovasculitis, dystrophic changes in neurons and massive hemorrhages. Similar morphological signs can be found at different stages of brain hypoxia / ischemia, the development of inflammatory processes and immune / autoimmune diseases [12, 13, 25, 29-31]. Signs of neuronal damage in those who died from COVID-19 were characterized by nonspecific changes in nerve cells – acute edema of neurons against the background of perivascular and pericellular edema; local damage to neurons and glial cells; edema and damage to neurons and glia; as well as the mitochondria of these cells; Kary cytolysis, which manifested itself as chromatolysis, swelling of the nucleolus, and displacement of the nucleus to the periphery of nerve cells [12, 13, 25, 29, 31]. The severity of these changes reached a maximum in the area adjacent to the necrosis focus, where all neurons were destroyed [25]. Analysis of autopsy protocols and brain autopsy material from deceased patients with lifelong confirmed COVID-19 infection showed that ultrastructural pathological changes in COVID-19 include those characteristic of any typical pathological process associated with hypoxia / ischemia, inflammatory processes and development of immune / autoimmune diseases [30, 31]. Thus, morphological changes in the brain in patients who died from COVID-19 indicate damage to the central nervous system, which also occur: against the background of hypoxia / ischemia, activation of free radical processes (oxidative and nitrosative stress) and associated local damage to neurons and glia, as well as in case of damage to cell membranes and subcellular structures, in violation of the energetic function of mitochondria of nerve cells and ionic homeostasis [12, 13, 25, 29, 33-39]. Ischemic and hemorrhagic strokes in patients who died due to the action of COVID-19 are largely due to a combination of hypoxia resulting from respiratory failure, oxidative-nitrosative stress, an increase in the content of reactive nitrogen species and reactive oxygen species, which are exacerbated by the patient's risk factors – atherosclerosis of the arteries of the base of the brain and hypertension [33-39].

A Model of Glutamate (Glu) and NO-Generating Compounds ($NaNO_2$) Neurotoxicity

Structural and ultrastructural changes in brain neurons that we observed in animals: frogs Rana Temporaria, rats Wistar, and rats of Krushinsky-Molodkina audiogenic strain, when simulating hypoxia / ischemia, glutamate neurotoxicity, ischemic and hemorrhagic strokes are accompanied by hypoxia, violation of incranial pressure and inflamation [38-57]. Such studies are important because hyperstimulation of Glu-receptors hyphenated is a leading pathogenetic factor of neuronal damage incranial pressure, stroke and brain traumatic injury [58-69].

Similarity of structural and ultrastructural changes in the neurons of the frog *Rana Temporaria* brain, in *Wistar* rats brain with ischemic stroke and in the rats of *Krushinsky- Molodkina* line genetically predisposed to audiogenic epilepsy and hemorrhagic hemorrhages.

Structural and ultrastructural changes in brain neurons, observed by us in frogs Rana Temporaria, Wistar rats, when simulating ischemic stroke, and rats of the audiogenic line Krushinsky-Molodkina when simulating hypoxia / ischemia, glutamate neurotoxicity, ischemic and hemorrhagic strokes, violation of intracranial pressure, inflammatory reactions and an increase in the content of reactive nitrogen species (RNS) and reactive oxygen species (ROS) [36-55]. Such studies are important because hyperstimulation of Glu-receptors hyphenated is the leading pathogenetic factor of neuronal damage, with increased intracranial pressure, stroke, and traumatic brain injury [56-69]. These phenomena occur against the background of exitotoxicity caused by Glu and an increase in the content of NO-generating compounds ($NaNO_2$) (Figure. 4) [34-39, 66-74]. Similar disorders of neurons and glial cells occur under the influence of various strains of COVID-19 in humans [5-9, 16, 17, 22, 24, 29, 30]. Thus, it can be assumed that some (but not the only!!!) phenomena characteristic of the above pathologies are the following factors: oxidative and nitrosative stress; an increase in the content of reactive nitrogen species (RNS) and reactive oxygen species (ROS); damage of cells, subcellular structures under the influence of nitrogen dioxide (NO_2), OH-radicals and peroxynitrites [74-94].

Violation of the cycles of nitric oxide and superoxide anion radicals leads to the appearance of highly reactive compounds: reactive nitrogen (RNS) and oxygen species (ROS).

Such processes, as a rule, occur when the regulatory mechanisms associated with the cycles of nitric oxide and superoxide anion radical are disturbed (Figure. 5) [84, 85, 88, 93, 94]. Therefore, as an aphorism, we cited the words of great scientists, which reflect, from our point of view, the essential mechanisms underlying a variety of diseases (a kind of "common denominator" of many diseases), including COVID-19. People whose regulatory mechanisms function within the physiological limits tolerate COVID-19 relatively easily. Perhaps one of the reasons, that healthy children are more resistant to the effects of COVID-19, and older people with chronic diseases, on the contrary, are more susceptible to irreversible changes, including death, is a reflection of the above. Undoubtedly, it is better to be healthy and rich than poor and sick. Whether this is good news and how encouraging it – is a big question. However, scientists and doctors know how to reduce the influence of this nonspecific com-

ponent, which is characteristic of many pathological processes, including those developing during hypoxia / ischemia, glutamate neurotoxicity, traumatic brain injury, as well as ischemic and hemorrhagic strokes. For this, first of all, it is necessary to slow down the phenomena of oxidative and nitrosative stress, during which the concentration of reactive nitrogen species (RNS) and reactive oxygen species (ROS) – nitric oxide (NO), nitric dioxide (NO_2), peroxynitrite anions ($ONOO^-$), which after protonation (addition of H^+) transform into an unstable form (ONOOH), which decomposes into NO_2 and OH-radicals. These studies complemented the data obtained by pathologists, morphologists and biochemists in other countries, including China, the United States, the United Kingdom and the European Union.

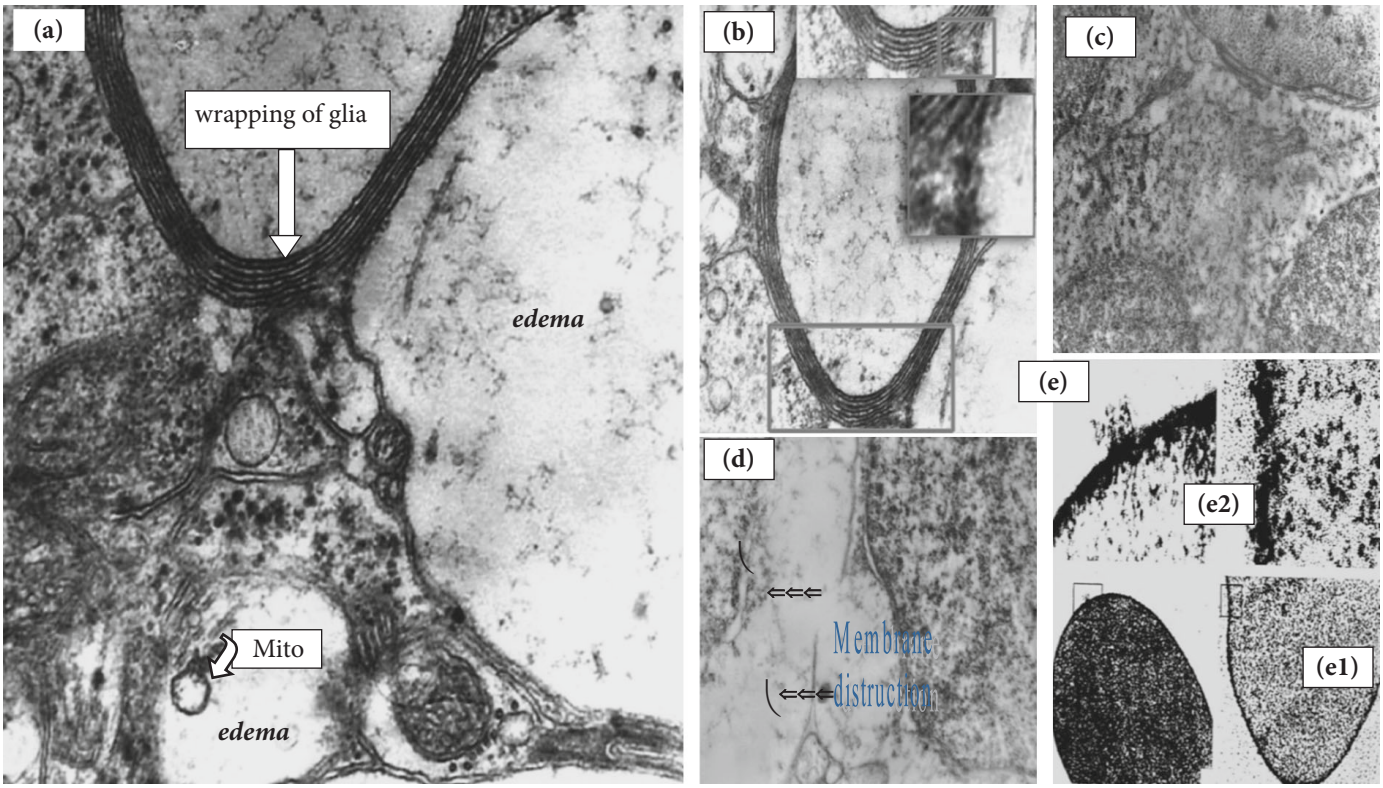

Figure 4: ***The typical pathological process associated with morphological/ultrastructural changes***

A model of glutamate (Glu) and NO-generating compounds ($NaNO_2$) neurotoxicity. Ultrastructural changes of granular neurons, glial cells (a, b, c) and mitochondria (a, Mito) under influence of glutamate (Glu, 1 mM, 1h) and NO-generating compound ($NaNO_2$, 1 mM, 1 h) (d), e – erytrocytes after action of $NaNO_2$ (1 mM, 1h) Nonspecific disorders and lesions in cells and subcellular structures: (a) edema of cells, mitochondria (Mito) and (b–e) local membrane lesions: (b) alterations in glial cells, which form multilayer wrappings around the areas of edema and neuronal damage (damage areas are shown in insets); (c, d) alterations in a layer of cerebellar granule cells (from local lesions to cell fusions); (e) a redistribution of proteins from a soluble state to a membrane-associated state in erythrocytes and local damage to erythrocyte membranes [38].

Electron microscopic photographs of neurons and glial cells (astrocytes) after toxic exposure to compounds that generate Glu and NO show edema and local membrane damage, changes in glial cells that form multilayered membranes around areas of edema and neuronal damage (areas of damage are shown in the insets); changes in the membrane-associated state of erythrocytes (e1)and membrane damage (e2) under the action of an NO-generating compound ($NaNO_2$, 1 mM, 1 h). The formation of a highly toxic product of nitrogen dioxide (NO_2, peroxynitrite - $ONOO^-$ - an oxidizing and a nitrating agent) disrupts the production of energy by mitochondria, disrupts the work of membrane pumps, which contributes to the development of edema and changes in intracranial pressure. Simultaneously with the destructive processes, there is a compensatory mechanism for protecting neurons from the harmful effects of hypoxia. The multilayer wrapping of neurons with glial cells is one such defense mechanism that prevents the release of proteases and phospholipases from neurons. Using a simple model of erythrocytes, it was shown that nitric oxide (NO) provides a de¬fense mechanism (redistribution of protein from the cytoplasm to membranes), and nitrogen dioxide (NO_2) causes local membrane damage. The data obtained can serve as a strategic basis for the selection of markers of brain damage after pathology with intracranial pressure, stroke, traumatic brain injury, and, possibly, will be used as a model of neuronal damage when exposed to COVID-19.

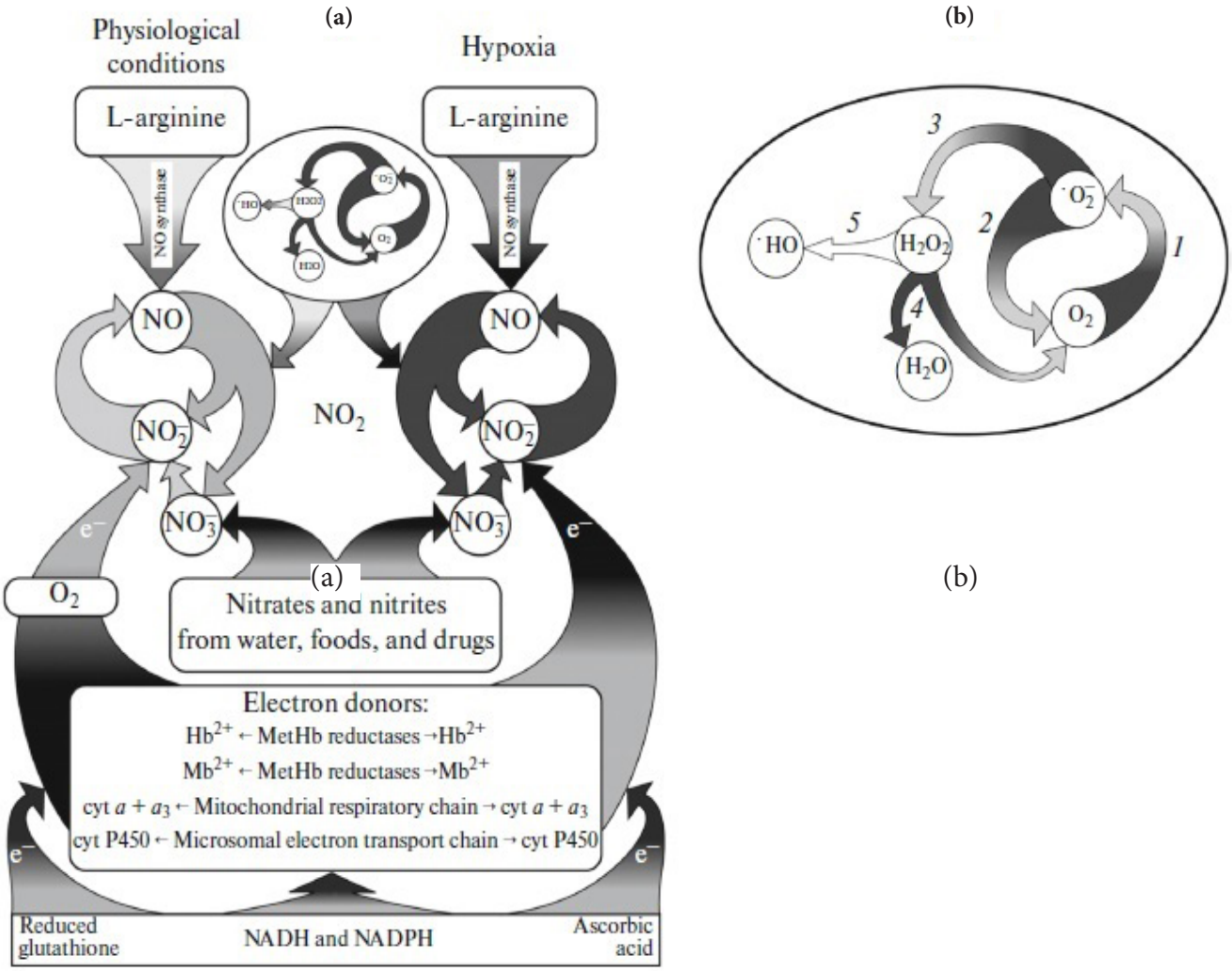

Figure 5: ***Cycle of nitric oxide (a) and superoxide radical anion (b) [98].***

In the nitric oxide cycle, one can distinguish the NO-synthase component ("L-arginine - NO"), which synthesizes NO in the presence of oxygen, and the nitrite reductase component, the activity of which sharply increases under conditions of oxygen deficiency (hypoxia / ischemia). The formation of NO with the participation of the NO-synthase component is carried out as a result of the oxidation of the guanidine nitrogen of L-arginine. NO_2^-, ions, formed from L-arginine, can again, with the participation of nitrite reductase systems, including Hb, Mb, cyt a + a_3 and cyt P-450, In addition to these electron transport systems (chains), ascorbic acid and reduced glutathione can play an important role in the reduction of NO_2^- ions. In the cycle of superoxide radical anion occur: 1 – reduction of oxygen (O_2) and the formation of superoxide anion radical ($\bullet O_2$); 2 and 3 – superoxide dismutation reactions catalyzed by superoxide dismutase; 4 – decomposition of hydrogen peroxide (H_2O_2) into water (H_2O) and molecular oxygen (O_2), carried out by the enzyme catalase; 5 – hydrogen peroxide (H_2O_2) 5 – hydrogen peroxide – H_2O_2 – also decomposes to form two molecules of the OH-radical. The cyclic organization of reactive nitrogen and oxygen forms ensures the conversion of these reactive, highly reactive compounds into less active substances. When the cycles of nitric oxide and superoxide anion-radical are disrupted, even more active molecules of nitric dioxide and peroxynitrites appear, again decaying into NO_2 and OH-radicals, which damage the main components of living organisms. Therefore, as an aphorism, we cited the words of great scientists, which reflect, from our point of view, the essential mechanisms underlying a variety of diseases (a kind of "common denominator" of many diseases), including COVID-19.

A typical pathological process associated with hypoxia / ischemia, inflammatory processes and the development of immune / autoimmune diseases is characterized by nonspecific changes that occur in various cells and subcellular structures

Officially, to date, there is no specific treatment for coronavirus infection. Treatment is symptomatic and aimed at eliminating nonspecific changes in the body caused by the coronavirus infection COVID-19. Nonspecific changes in cells and subcellular structures that occur in COVID-19 and other pathological processes developing during hypoxia / ischemia, inflammatory processes of autoimmune / immune diseases, create a kind of «common denominator» for almost all currently known pathological processes and diseases. Structural and ultrastructural changes in cells and subcellular structures in the above numerous pathological processes and diseases are characterized by a) *local damage of cell membranes* and *subcellular structures;* b) *the development of edema in cells and subcellular structures (for example, mitochondria)*; c) *disturbances in energy processes*; d) *a decrease in the content of ATP, GTP and other high-energy*

substrates; e) *a decrease in the value of the mitochondrial potential*; g) *disturbances in the work of Na^+ / K^+ and Ca^{2+}-ATP-ases etc.*

Previously, we proposed a generalizing concept of the development of pathological processes, according to which a typical pathological process is based on nonspecific violations of cyclic regulatory processes, when the content of reactive nitrogen and oxygen forms simultaneously increases and NO_2 and peroxynitrites, capable of oxidizing unsaturated fatty acids that are part of cellmembranes and subcellular structures; oxidize and damage DNA/RNA guanine bases; oxidize SH-groups of amino acids and proteins, and also participate in the nitrosylation of tyrosine residues of proteins [38, 93, 98]. The mechanisms of changes in the body established to date have allowed the researchers to conclude that changes caused by excessive activity of normal processes and reactions develop in the course of many pathological processes (especially in their early stages). Many pathological processes at their early stages consquently differ from normal physiological processes only in having developed in the wrong place, at the wrong time, or with the wrong intensity. The idea agrees well with the views that many pathologies start with a failure or distortion of regulatory mechanisms. COVID-19 is no exception in this regard. The formation of a highly toxic product of nitrogen dioxide (NO_2) , peroxynitrite - $ONOO^-$ /NO_2 – an oxidizing and a nitrating agents) disrupts the production of energy by mitochondria, disrupts the work of membrane pumps, which contributes to the development of edema and changes in intracranial pressure. Simultaneously with the destructive processes, there is a compensatory mechanism for protecting neurons from the harmful effects of hypoxia. The multilayer wrapping of neurons with glial cells is one such defense mechanism that prevents the release of proteases and phospholipases from neurons. Using a simple model of erythrocytes, it was shown that nitric oxide (NO) provides a defense mechanism (redistribution of protein from the cytoplasm to membranes), and nitrogen dioxide (NO_2) causes local membrane damage. The data obtained can serve as a strategic basis for the selection of markers of brain damage after pathology with intracranial pressure, stroke, traumatic brain injury, and, possibly, will be used as a model of neuronal damage when exposed to COVID-19.

General Conclusions

The purpose of this article was to show that normal physiological cyclic mechanisms can be the foundation for the body's ability to tolerate any pathological processes, including COVID-19. Our views are consistent with the earlier views of the classics of medicine – Rudolf Virchow and physiology – Leon A. Orbeli. Our contribution to understanding these mechanisms is that we have proposed the concepts of nitric oxide and superoxide anion radical cycles [38, 88, 90, 93, 94, 95]. These cycles, according to our data and developed concepts, protect the body from damage by highly reactive compounds that are formed in any pathology associated with hypoxia / ischemia, inflammatory processes, immune and autoimmune diseases, as well as COVID-19 [38]. The cycles of nitric oxide and superoxide radical anion are a consequence of the cyclic principle and the holographic principle, which, together with the atomic principle of the existence of matter, constitute the fundamental basis for the unity of living and inanimate matter [95, 96].

Over the past decades, we have suggested that the cyclic organization NO and $\bullet O_2^-$ in cells and in the whole organism may be a consequence of the existence of such a principle, the universality (or globality) of which is comparable to the principle of the atomic structure of matter. This principle extends its influence to almost all structural and functional levels in animate and inanimate nature, subordinates the behavior of living subjects and inanimate objects, and, sets the rules for the functioning of all regulatory systems that contain elements of negative and positive feedback.

Analysis and synthesis of literature data allowed us to formulate rules of conduct during the COVID-19 pandemic [1-22, 75-79, 97-101]. It is possible that our other colleagues will share with us, support some points of these rules and add some of them with their own points.

Self-Isolation and Quarantine are Considered Some of The Best Anti-COVID-19 Remedies in 2021.

The measures below can be protective measures to reduce the likelihood of contracting COVID-19 and the occurrence of death for the entire population. 1) Limiting to a minimum of participants in communication (voluntary self-isolation); 2) glasses and a screen to protect the mucous membrane of the eye, as well as masks / respirators to protect the nasopharynx; 3) using antiviral ointments before going outside and rinsing the nasopharynx after visiting public places; 4) taking ascorbic acid, which activates the synthesis of endogenous interferons, and instilling recombinant interferons into the nose after visiting public places where there is a high probability of contact with infected people; 5) gloves and hand sanitizers; 6) use of vaccines approved by national health ministries and WHO; 7) use / application of anti-inflammatory and antioxidant agents at all stages of the development of COVID-19; 8) prevent an increase in blood clotting above the physiological norm; 9) always have anticoagulants with you; 10) keep in mind that relatively cheap antiparasitic drugs used in different countries of the world have reduced mortality from COVID-19 by 3 or more times, despite the fact that these drugs are not officially recognized drugs for COVID-19.

Protective Action of Iveromexin (Ive). It Would be Fatal Mistake Not to Use Ive:

IVERMECTIN (IVE) is a broad-spectrum antiparasitic agent, applied in Delhi (India) since April 20, eliminated the COVID-19 crisis. The incidence decreased by 97% in 6 weeks. It would be a fatal mistake NOT to use IVE. They used it and it saved Delhi. Unfortunately, Tamil Nadu (state in the south of India) did not, and their state was devastated. Their new cases increased from 10 986 to 36 184, i.e. threefold. Their refusal to use willows harmed them. Not only did the incidence in Tamil Nadu reach the highest level in India, but the number of their deaths rose sharply from 48 on April 20 to 474 on May 27 – a tenfold increase [24].

Russia Presented a 4 types of COVID-19 Vaccines and Ready to Help Other Countries Fight the Pandemic:

Russia presented a drug for the treatment of coronavirus, created on the basis of the antimalarial drug Mefloquin. This drug was developed back in the 70s of the last century and is included in the list of essential medicines recommended by the World Health Organization (WHO) for the treatment and prevention of malaria. But since it is necessary to find an effective remedy to help patients with coronavirus in the shortest possible time, doctors around the world have started testing existing drugs developed for other purposes, in the hope that they will help with COVID-19. And finally, it is worth recalling once again that Russia has 4 types of COVID-19 vaccine and is ready to help other countries fight the pandemic.

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