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Mini Review

COVID-19 Spread Chain Reactions

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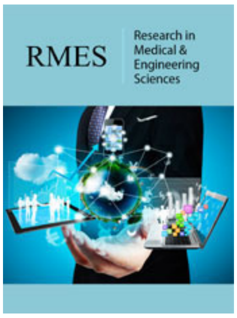
ISSN: 2576-8816



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Submission: January 17, 2024

Published: January 29, 2024

Volume 10 - Issue 5

How to cite this article: Mansurov ZA, Kurmanbekov AS, Nazhipkyzy M*, Kapysheva UN and Cherednichenko OG. COVID-19 Spread Chain Reactions. Res Med Eng Sci. 10(5). RMES.000748. 2024. DOI: 10.31031/RMES.2024.10.000748

Abstract

In this mini review, a comparative analysis of various stages of the development of COVID- 19 infection in the human body is carried out in terms of chemical chain reactions. The main stages of the development of infection in the body and forms of the disease, such as asymptomatic, mild and severe, proceed similarly with various types of chemical chain reactions: unbranched, branched and degenerate-branched reactions. The rate of spread, infection and reproduction of the SARS- CoV-2 virus in a living organism was assessed in comparison with the rate of chain chemical reactions. A direct parallel has been revealed between the course of various stages in the development of a coronavirus infection with the "Theory of Chain Reactions". Based on the analysis of the available data, a new hypothesis for the spread and course of the disease of coronavirus infection has been put forward. As in the cases of the chain reaction process, when the introduction of inhibitors into the system can stop the course of reactions, timely adequate drug therapy can prevent the spread and disease of COVID-19 infection. Coronavirus infection cannot reduce immunity it rather disrupts the regulation of the body's immune response, thereby causing a number of failures. In this regard, the role of immunity, the immune response to the penetration of a foreign agent into the human body, was studied and the results were compared with various stages of chemical reactions: Chain initiation or initiation, chain development and termination. As in the case of branched chain reactions, when the interaction of one active particle with the original molecule is accompanied by an avalanche-like growth of new chains and reactions in several directions, starting from a single radical atom, with the formation of many products of the process, the severe course of COVID-19 disease can activate the entire immune system. system and immune response, which will cause a cytokine storm and a cascade failure in the functions of various human organs. Taking into account the large negative value of the inflammatory reaction - cytokine storm in the case of this infection, the use of superoxide radical can suppress the activity of the SARS-CoV-2 virus and significantly maintain the balance of antioxidants and oxidants in the human body. At the same time, the superoxide radical can suppress the activity of the cells of one's own immune system, which will allow one to restrain the level of cytokines, and, accordingly, avoid a cytokine storm in a patient and trigger an antiviral immune response, which may be useful and may significantly improve the course of the disease. It is proposed to study the behavior of radicals using the electron paramagnetic resonance (EPR) method for COVID-19. It has been hypothesized that the use of superoxide radical for the treatment of patients with COVID-19 may be more effective than traditional drug treatment.

Keywords: Chain reactions; COVID-19; Immunoglobulin; Mild; Radicals; Cytokine storm

Introduction

The article provides a qualitative analysis of the development of COVID-19 in terms of chain reactions, and the need to determine the characteristics of the disease and viruses to create a more complete chain mechanism. In April 2020, the article "The Chain Reaction of COVID-19" was published under the authorship of Kim R. Sawyer (DOI:10.13140/RG.2.2.31018.98240). Unfortunately, this article only provides general considerations of the author about the chain nature of the spread of coronavirus. Today, COVID-19 (Corona Virus Disease 2019-coronavirus infection of 2019) is an important, if not the main problem of all countries of the world. The coronavirus pandemic has seriously shaken the population and the economy of the countries, this resulting in to the temporary (in some cases, complete) closure of enterprises in the countries with a high percentage of cases, sharply increasing the price of everyday products, speculation certain goods: antiviral drugs, sanitary masks, disinfectants.

It is believed that the pandemic of the coronavirus infection COVID-19 has far-reaching severe economic consequences, as the State allocates huge financial resources to stop the spread of the virus, treat patients with the infection and support citizens. The medicine of the countries of the world is undergoing the strongest tests of strength. The coronavirus has shown how important the medical profession is. At the risk of their lives, medical professionals and epidemiologists are fighting a little-known infection. It would seem that quarantine measures, restrictive measures and strict compliance with sanitary requirements in a state of emergency were supposed to contain the spread of the coronavirus around the world and save the lives of citizens. However, due to new outbreaks of infections (so-called waves), the number of infected people and those dying from the disease does not decrease. Now scientists and doctors around the world are studying and actively exchanging new tactics and methods of treating coronavirus infection. However, unfortunately, there are quite a lot of contradictory data in the literature, including scientific problems concerning COVID-19. This may be due to the fact that the virus is predisposed to frequent mutations and the appearance of more aggressive mutant forms. In [1], it is stated that for an infection caused by the SARS-CoV-2 virus, the incubation period is 1-14 days. The disease can take an asymptomatic, mild or severe course, with a risk of death, but a full clinical picture is not t clear yet [2]. Chinese scientists suggest that 80% of the world's cases of coronavirus infection are mild or asymptomatic. 15% is the average, which requires oxygen therapy. The remaining 5% are patients in critical condition who need artificial lung ventilation [3-8].

The authors of this article, being chemists by training, observing a certain similarity in the course of the stages of the disease of coronavirus infection with the "Theory of chain reactions" of Semenov [9], put forward a hypothesis of the spread and course of the disease in people with COVID-19. Chain chemical reactions are reactions that occur with formation of free radicals that can convert reagents into end products, maintaining the constancy of free radicals or even increasing them (branched chain reaction). Free radicals are highly reactive active particles containing one unpaired electron and having unsaturated valences [8]. In chain chemical reactions, there are three stages: The initiation or nucleation of the chain (occurs under the influence of certain factors), its development (the interaction of a free radical with a reagent molecule, followed by formation of the reaction product) and chain breakage (the death of active particles, free radicals) [9]. Judging by the picture of the spread of the epidemic, SARS-CoV-2 in the human body triggers a process that leads to a sharp increase in the viral load affecting various organs, which is strikingly similar to a chemical chain reaction. In the case of serious complications, the disease and the spread of the virus can only be stopped by drug therapy, as in the case of the introduction of inhibitors into the chemical reaction. In the case of chain chemical reactions, when free radicals react with a new agent each time to form a new product, the coronavirus infection also spreads from one person to several, etc., thereby expanding the area of infection. One radical is enough to start a chemical reaction and one COVID-19 patient is enough for the disease to move into the category of a global pandemic. The rate of spread, infection and reproduction of the virus in a living organism is very high, as is the rate of reaction in chain chemical reactions.

The course of the disease largely depends on the general state of health of the patient. In most cases, with an asymptomatic course of the disease, a person may not know that he has been infected with the virus. This is due to the fact that the patient has a strong immune system that protects the body from infections, toxins and malignant cells, not only from COVID-19, but also all seasonal, acute respiratory viral infections [10]. After infection with the virus, the human body fully activates immunity, which is the body's response to a foreign agent in the form of immunoglobulins (antibodies) in special proteins that are involved in the immune response. Immunoglobulin A (IgA), which is an indicator of the state of humoral immunity, is one of the first to react to the ingestion of SARS-CoV-2 in the human body. A large number of these antibodies are present not in the blood, but on the surface of the mucous membranes and various fluids that wash the epithelium: saliva, urine, bronchial secretions, breast milk and other liquid media. The function of the IgA is to bind to harmful agents and thereby prevent more spread and thus damage to healthy human cells. A decrease in the amount of IgA in the body means that the immune system is deficient [11]. Subsequently, the "signal" immunoglobulin M (IDM) is produced, which is a sign of acute infection and the course of the acute phase of the disease. When the virus enters the body, the antibodies form complexes with them, activate the complement system, resulting in increased phagocytosis [12]. Immunoglobulin G(IgG) is a fraction of blood proteins that provide a protective function not only in the blood, but also in the extracellular space and tissues. The main task of IgG is to identify pathogenic organisms and measures to eliminate them, by activating phagocytosis and forming unique protein components, the action of which is aimed at eliminating the pathogen [13].

In order to understand how COVID-19 spreads, it is necessary to have an idea about the chain chemical reaction. Chain reactions play an important role in many branches of chemistry, in particular in photochemistry, combustion chemistry, explosions, nuclear fission and nuclear fusion reactions, and in organic chemistry. There are several types of chain reactions: unbranched, branched and degenerate chain reactions. With COVID-19, there are also several types of the disease courses: asymptomatic, mild, and severe (critical) coronavirus disease form. Some scientists and doctors also determine the course of the disease of moderate severity, in which the infection passes lower into the lungs, so the symptoms of respiratory diseases, such as cough, are more pronounced. However, in many cases, the disease of moderate severity is transient and without proper medical intervention quickly passes into a severe (critical) stage [14].

The asymptomatic course of the covid-19 disease in comparison with the unbranched chain reaction

An asymptomatic course of coronavirus disease, in which COVID-19 can be completely invisible to a person, since it proceeds without symptoms. However, there is evidence of mild weakness and loss of sense of smell in humans, with no other symptoms, which is also a symptom. However, the conducted studies show that one of the main reasons for the rapid spread of COVID- 19 is the asymptomatic course of the disease [15] (Figure 1). In the case of an asymptomatic disease, the infection lives for a certain time on the mucous membrane, then the human immune system reacts to the virus (IgM), produces proteins and antibodies (IgG), which destroy the virus, finish the infectious process [16]. In unbranched chain reactions, in each elementary reaction act, one active center is formed from one active center, which can be considered by the example of a photochemical reaction between hydrogen and chlorine. In this reaction, the chlorine molecule, absorbing a quantum of light, decays into two atoms. Each of the resulting chlorine atoms begins a chain of chemical transformations; in this chain, the chlorine and hydrogen atoms act as active particles. Chain breakage occurs as a result of a reaction between atomic hydrogen and oxygen molecules with the formation of a low-activity radical HO_2, which does not react with the initial molecules under conditions of not very high temperatures [17]. Thus, the above suggests that the asymptomatic course of the disease is very similar to the mechanism of unbranched chain chemical reactions.

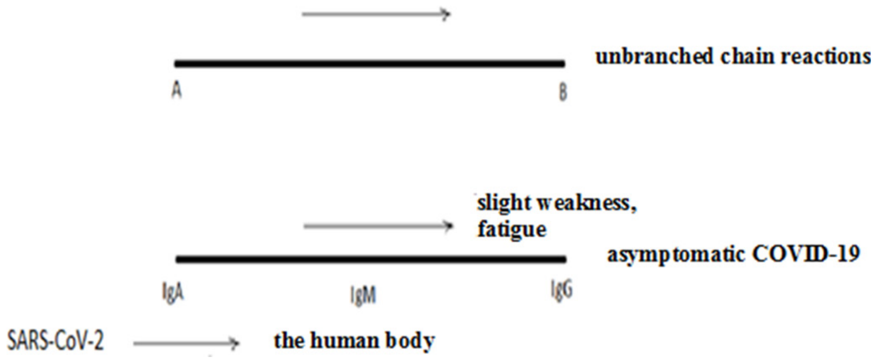

Figure 1: Comparison of asymptomatic COVID-19 with unbranched chain reactions.

Mild course of covid-19 disease compared to degenerate chainreaction

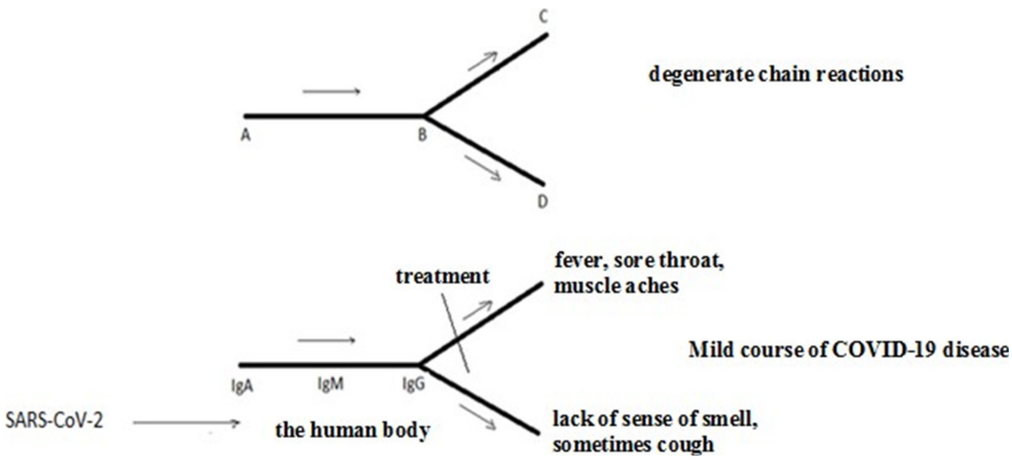

Figure 2: Comparison of mild COVID-19 disease with degenerate chain reactions.

The mild course of the coronavirus disease, in which only the upper respiratory tract is affected, is similar to the flu or colds. There is a slight fever, mild headache, increased fatigue, sorethroat, coughing, aching muscles, slight signs of a cold, pallor, chills. In many cases, with a mild form of the disease, the symptoms disappear after a week or two, which indicates a high immune response and timely medical treatment [18] (Figure 2). However, there is information that a mild form of coronavirus can also lead to serious consequences for the body. This is the conclusion reached by the British researchers of the cover scan group. They examined more than 200 patients who had a mild course of COVID-19, and found that almost 70% had abnormalities in one or more organs after recovery. In particular, we are talking about the lungs, heart and pancreas. The virus also often affected the kidneys, liver and spleen. This is called immune-mediated lesions [19]. According to the mechanism, the vast majority of oxidation processes refer to the class of free-radical chain reactions with degenerate branching. Semenov [9] suggested the presence of so-called chains of degenerate branching, the essence of which is that as a result of the primary reaction,an intermediate relatively stable compound is formed and accumulates to a critical concentration, which can later decompose independently of the main reaction, giving rise to new chain reactions. For example, when some compounds are oxidized, peroxides are formed, which themselves are ableto decompose under certain conditions to form active particles free radicals. The result is branchingof the chains, although not so fast: after all, in order for the peroxides to decay at a noticeable rate, they must first accumulate. Such processes were called degenerate ramifications. Semenov [9] called this type of chain reactions degenerate chain reactions, and ramifications due to intermediaterelatively stable products-degenerate ramifications [20].

If we compare the mild course of COVID-19 disease with degenerate chain reactions, we cansee some similarity in the mechanism of the reaction. With a mild course of the disease, the person'sown immune system actively fights the virus with medication. Thus, the virus particle is eliminatedand the chain of distribution among the population is broken. In this case, there may be consequencesin the form of deviations in the work of some organs after recovery. In degenerate chain reactions, the rate of decomposition of products into radicals is much less than the specific rate of continuationof the chain by the active centers, as a result of which the reaction can be stopped by introducing aninhibitor.

Severe course of covid-19 disease in comparison with branchedchain reactions

After the virus enters the cell of the body, actively reproduces and spreads, the immune systemturns on another protective reaction, which is expressed in the excessive release of cytokines. That causes a cytokine storm an uncontrolled inflammatory reaction in the body, in which the level of cytokines in the blood increases dramatically, causing damage to the body's own tissues and organs (Figure 3). There is literature evidence that for the development of systemic inflammation, i.e. cytokinestorm in COVID-19 in cells and tissues, one of the responsible factors is free radicals reactiveoxygen species from mitochondria, which are executive factors for causing direct damage to cellsand several organs. However, the sources are very contradictory and there is no complete answer to the question of how free radicals are involved in the process as a damaging agent that kills cells, orsimply as a signal system of delivery. In some cases, free radicals are used as a system with a high penetrating power, which has the ability to transmit massed signals to certain cells and tissues [21]. During a cytokine storm, the immune system begins to work at maximum capacity to fight the infection, and as a result, the tissues of the inflammatory focus are destroyed, and the inflammation spreads to neighboring tissues. Over time, the cytokine storm engulfs the entire body, and everythingcan end in the death of the patient. This condition of the patient is called a severe (critical) course ofthe coronavirus disease. Basically, the disease occurs with respiratory failure and extensive inflammatory process, pneumonia and failure of other vital organs functioning [22]. In these cases, for the treatment of a patent seriously ill with COVID-19, it is necessary not only to destroy the viruses in the body, but also to apply adequate medication to reduce the level of cytokines. In the late 20s of the last century, Semenov [9] estate the existence of branched chain reactions, in which the interaction of one active particle with the original molecule leads to the formation of two or more new active particles. Thus, the reaction can proceed in an avalanche-like chain build-up in several directions, starting with a single atom, a radical with the formation of many products of the process [23].

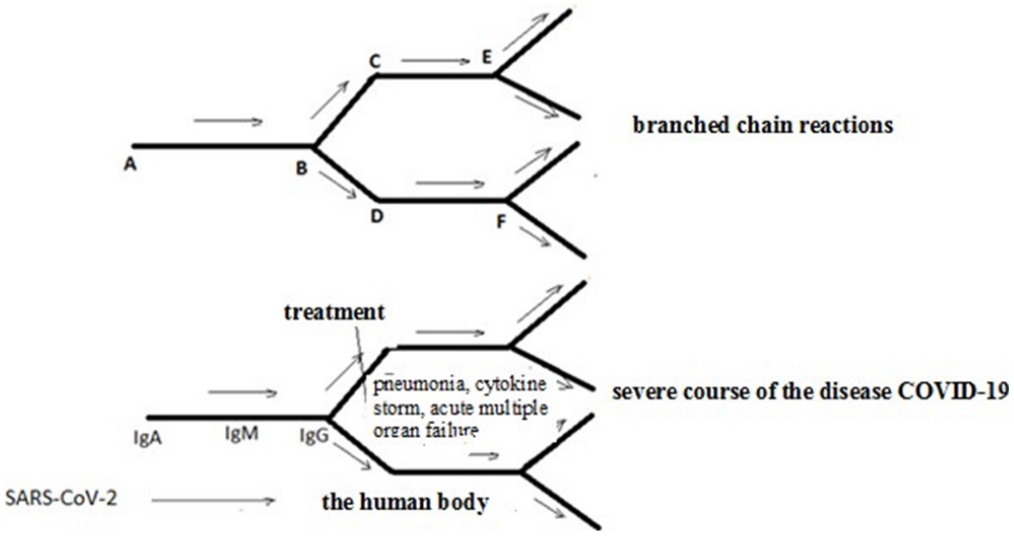

Figure 3: Comparison of severe course COVID-19 with branched chain reactions.

The role of oxygen in the treatment of covid-19

To date, there is an opinion that there is no need to interfere with the work of the immune system after a human being get infected with COVID-19. In the asymptomatic course of the disease with an infection, there is no need to interfere with the work of the immune system, since the immunesystem in the form of antibodies itself eliminates the virus, thereby breaking the chain of spread. In other cases, high-quality medical intervention with adequate therapy is necessary. In frequent cases, to save a person, it is necessary to connect a seriously ill person to a lung artificial respiration device (ventilator) to facilitate the movement of air into/out of the lungs or to an oxygen concentrator with a higher concentration of oxygen than in the ambient air. All this is done in order to solve the problem of respiratory failure in pneumonia caused by COVID-19 and topreserve the maximum volume of lung tissue. Hence the conclusion of specialists: to save seriouslyill patients, it is necessary (in accordance with approved treatment protocols) to use various combinations of medications, with constant monitoring of the level of oxygen in blood (saturation),in the case of oxygen starvation of the body, connect the patient to oxygen supply devices [24]. In the fight against COVID-19 infection, all possible treatment methods must be consideredbased on the complex pathophysiology of this viral infection. In the work [25], it is proposed to usein the treatment of COVID-19, in addition to drug therapy, also oxidative reactions and ozonetherapy, to improve blood flow in small vessels (capillaries), as well as the supply of oxygen to cells.Oxidative reactions in our body are a necessary function of the immune system, which takes electrons from bacteria, viruses and other pathogens and thus prevents the development of infection in the body. During respiration and biological reactions with free molecular oxygen, the so-called "superoxide radicals" are formed. Free superoxide radicals are present in any organism, their role isto destroy infectious cells, and since free radicals are very active, when they increase in number, there is a danger of destruction of healthy cells of the body by them [26].

In a normal state, the balance of antioxidants and oxidants is sufficient in a healthy lung. The tragedy with COVID-19 is that superoxide converts the ferrous iron of the heme protein to ferric iron and the formation of iron superoxide occurs. Thus, the transfer of oxygen by the iron to the tissues becomes difficult and the patient suffers from respiratory failure and oxygen treatmentmay not help the patient [27-33]. A person, like any multicellular organism, has to fight against microbes and viruses that havegot inside his body and into the blood. This fight is carried out by specialized cells-phagocytes, which include granulocytes and monocytes of the blood, as well as tissue cells macrophages. All these cells, coming into contact with the surface of the cells of bacteria and virus, begin to vigorously release free radicals as a result of the transfer of an electron from the NADPH-oxidase enzyme complex embedded in the phagocyte membranes to the dissolved molecular oxygen.

$$NADPh_{(intracellular)} + 2O{=}O_{(extracellular)} \rightarrow NAD^{+}_{(intracellular)} + H^{+}_{(intracellular)} + 2(^{\bullet}OO^{-})_{(extracellular, superoxide\ radical)}$$

NADPh- Nicotinamide Adenine Dinucleotide Phosphate;

NAD- Nicotinamide adenine dinucleotide.

In this case, each NADPh molecule, when oxidized, gives up two electrons one after the other to two oxygen molecules, resulting in the formation of two anion radicals of superoxide. The reaction catalyzed by NADPh oxidase consists in the oxidation of NADPh•H to $NADPh^{+}$ inside the cell with the transfer of electrons to the other side of the cell membrane and the formation of a superoxide radical from the oxygen of the medium on the outer side of the cell. Thus, the immune system itself produces oxygen radicals and destroys harmful agents in the body [34,35]. However, superoxide radicals can harm both the phagocytes themselves and other blood cells, and, of course, the viruses that caused the activation of the macrophage. Naturally, all these cells try to get rid of superoxide radicals, for that, they produce enzymes called superoxide dismutase. Differing in the structure of the active site and the structure of the polypeptide chain, all superoxidedismutase catalyze the same superoxide radical dismutation reaction:

$$OO^{-} + {^{\bullet}OO^{-}} + 2H^{+} \rightarrow O_2 + HOOH \text{ (hydrogen peroxide)}$$

However, there are also positive aspects of superoxide radicals, such as the destruction of lipidcompounds that are deposited on the walls of blood vessels, preventing the occurrence of many diseases of the cardiovascular system, stimulating the appearance of new cells and contributing to the death of old and sick ones, correcting the resonant frequency of cells, stimulating the brain, increasing the overall tone of the body, maintaining the immune system at the right level [36].

The role of immunity in covid-19

In order to understand what processes occur with the human immune system when SARS- CoV-2 enters the body, it is necessary to consider some aspects of immunology. Viruses are obligate intracellular parasites that cause infection by invading the body's cells. Their life cycle includes a relatively short extracellular period and a longer intracellular period during which they undergo replication. The immune system has non-specific and specific mechanisms that attack the virus at both phases of its life cycle. The immune system has various mechanisms that prevent the activation of the immune systemthat potentially damages tissues, for example, anti-inflammatory cells (regulatory T cells, myeloid suppressor cells), anti-inflammatory cytokines (TGF-β, IL-10) and anti-inflammatory small molecules (adenosine, lipoxins, vasoactive intestinal peptide/pituitary adenylate cyclase-activating peptide). Balancing these mechanisms can prevent over-activation of immune responses and, as a result, excessive tissue damage, but can also reduce immune responses to fight infectious pathogens,which will reduce the level of cytokine storm in the body. These immunoregulatory mechanisms arecrucial for controlling pro-and anti-inflammatory balance [37]. However, in SARS-CoV (the pathogenic agent of SARS) and SARS-CoV-2 shows a disproportion between antioxidants and free radicals or oxidants, leading to the oxidative stress is observed [38]. As it was mentioned above, the coronavirus is able to bind to an iron molecule that transportsoxygen as part of the hemoglobin molecule. Thus, the iron ion becomes a free molecule, and the hemoglobin molecule cannot bind to oxygen. Thus, the oxygen saturation of the body decreases andthe formation of free oxygen radicals in tissues and organs increases, i.e., typical oxidative effects occur.

Reactive oxygen species play a key role in the pathophysiology of acute respiratory distress syndrome (respiratory failure) in COVID-19. After a viral infection, the lung macrophages and endothelium are activated and regulate the surface expression of adhesion molecules by human blood cells. This leads to the activation of neutrophils and the subsequent transmigration of the intravascular space, where it produces a variety of inflammatory mediators, which include reactiveoxygen species such as super oxides, hydroxyl radical and Nitric Oxide (NO), cytokines and chemokines. In conditions of hypoxia caused by infection, the immune system suffers, since the oxygen levels in the tissues play a crucial role in regulating the immune response in both cancerousand inflamed tissues [39]. Cell proliferation requires a large amount of energy for the biosynthesis of each component ofthe daughter cells [40,41]. Many of these components, such as lipids, nucleotides, and amino acids,are products of oxidative metabolism. Consequently, the main link in antiviral immunity T-cells suspend proliferation in hypoxic conditions. Most *in vitro* studies indicate violation of T-cell proliferation, as well as cytokine production when stimulated by low oxygen concentrations [42-46]. Cell proliferation at the periphery is important for T-cell immunity. The T cell population consists of many types of T cells that can cover a wide range of antigens. Since only a tiny fractionof T cells can recognize a particular antigen, priming of resting T cells always starts with a small number of cells. However, the activity of T cells, especially cytotoxic CD8+ effectors, is based ondirect recognition of antigen-expressing cells; therefore, antigen-specific T cells must rapidly proliferate to a significant number in order to compete with fast-growing pathogens.

Native T cells are relatively rich in mitochondria and usually rely on oxidative phosphorylation, whereas activatedT cells regulate the aerobic glycolytic pathway, maintaining a high energy requirement for proliferation. In particular, for CD8+ T cells, *in vitro* studies have shown that hypoxia significantlyinhibits the development of cytotoxic T-cells (CTL), especially in terms of the number of CTL- induced cells [47,48]. A recent paper shows an increase in oxidative stress in T cells under hypoxicconditions, accompanied by a decrease in T-cell proliferation and an increase in T-cell apoptosis [49]. In accordance with this change, mitochondrial activity seems to be important for optimal activation of T-cells [50,51]. Mitochondrial metabolism produces super oxides, which in turn contribute to the activation of T-cells [52]. Although they are well known for their destructive effects on biomolecules, super oxides are increasingly accepted as essential components of signaling pathways and response modulators in physiological and pathological conditions [53]. ROS are known to mediate NF-kB activation [54,55], but chronic exposure to ROS inhibits phosphorylation and activation of NF-kB [56]. From the above, it follows that reactive oxygen species, first, can suppress the activity of cellsof the innate immune system, which will allow to restrain the level of cytokines and secondly, effectively launch an antiviral immune response.

Conclusion

With a higher degree of probability, it can be assumed that the spread of the virus in the humanpopulation proceeds in the form of chain reactions. The jumps of the COVID-19 disease (epidemic waves), which periodically cover the countries of the world, have an explosive character. The very process of the disease in severe cases is similar to branched chain chemical reactions and can occur in parallel in several directions. After entering the body, SARS-CoV-2 can affect all vital organs, such as the lungs, brain, nasopharynx, heart, blood vessels, liver, kidneys and intestines. The consequences of the disease can be very different and serious, from scarring of the lung tissue and kidney failure to inflammation of the heart muscle, arrhythmia, liver damage, cognitive impairment, psychosis, accompanied by a sharp change in mood. In the case of an asymptomatic disease, the human immune system can cope on its own, without medical intervention. In some cases, the disease may proceed more slowly, with the subsequent manifestation of some symptoms. After the use of adequate therapy to relieve or eliminate the symptoms of COVID-19, as in degenerate chain reactions, the process of infection and disease may stop. As with chain chemical reactions, the disease and spread of COVID-19 infection can be prevented by introducing inhibitors into the system. Despite the fact that there are a number of publications about the harm of the superoxide radical to the human immune system and organs, some responses of the human immune system show the effectiveness of this radical in destroying the virus and, accordingly, treating COVID-19. At the same time, the superoxide radical can suppress the activity of the cells of the own immune system, which will allow to restrain the level of cytokines, and accordingly will avoid a cytokine storm in the patient, and secondly, the superoxide being an active radical can effectively launch an antiviral immune response and destroy SARS-CoV-2. In a recently published article [57], the author came to approximately the same conclusions and made the assumption that each course of the disease for different people is different and the long-term COVID can be several disorders combined into one.

Some questions needed to clarify the connection of covid-19 withchain reactions

a) What determines the activity of the mutant strain in comparison with the native virus.

b) How do the structural differences and sizes of viruses affect their infectious activity, on the basis of which to obtain a number of virus activity ($V_1>V_2>V_3$....).

c) The role of the biradical oxygen molecule in the treatment of COVID-19.

d) What oxygen concentrations are necessary to improve the condition of patients, and afterwhat certain critical concentrations (saturation), oxygen begins to have a detrimental effect.

e) The need to study the activity of EPR spectroscopy.

The review article is prepared to draw the attention of doctors, epidemiologists,immunologists, scientists and specialists who are active in the fight against COVID-19 to the issuesof the disease, and to take measures to treat patients and prevent the spread of infections.

Author Contributions

Conceptualization: M.N. and A.K.; validation and formal analysis: Z.M.; investigation: A.K.; writing-original draft preparation: M.N. and A.K.; writing-review and editing: M.N. and A.K.; project administration: Z.M. All authors have read and agreed to the published version of the manuscript.

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.

Funding

None.

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