INOBVIOUS PATHOGENETIC LINKS OF MECHANISMS EFFECTS ON THE HUMAN ORGANISM OF THE SARS-COV-2 VIRUS

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The authors formulated a hypothesis about an important link in the pathogenesis of COVID-19, in which the increasing hypoxia and an acute response of the body like a general adaptation syndrome, accompanied by systemic pathological changes, including dangerous disorders of rheology and blood coagulation, play a key role.

Keywords: coronavirus, COVID-19, hypoxia general adaptation syndrome, cortisol immunity, neutrophils, monocytes, lymphocytes, cytokines

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НЕОЧЕВИДНЫЕ ПАТОГЕНЕТИЧЕСКИЕ ЗВЕНЬЯ МЕХАНИЗМОВ ВОЗДЕЙСТВИЯ НА ОРГАНИЗМ ЧЕЛОВЕКА ВИРУСА SARS-COV-2

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Авторами сформулирована гипотеза о важном звене патогенеза COVID-19, в котором ключевую роль играют нарастающая гипоксия и острая ответная реакция организма по типу общего адаптационного синдрома, сопровождающиеся системными патологическими сдвигами, в том числе опасными нарушениями реологии и коагуляции крови.

Ключевые слова: коронавирус, COVID-19, гипоксия, общий адаптационный синдром, кортизол, иммунитет нейтрофилы, моноциты, лимфоциты, цитокины

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Today, specialists in various fields of knowledge pay much attention to the problems associated with COVID-19, a new disease caused by the SARS-CoV-2 coronavirus that has grown into a developing pandemic. The volume of scientific information on COVID-19 is growing exponentially, but for obvious reasons there are still few works summarizing these scattered pieces of data.

This report puts up for discussion some theses of the hypotheses about one of the likely significant links in the pathogenesis of the disease caused by coronavirus. These theses and hypotheses were formulated based on the published information describing properties of SARS-CoV-2. Intentionally, their presentation is as succinct as the format of this brief report allows; sequentially, they are formulated as follows:

A. In many COVID-19 cases, coronavirus infection causes development of severe mixed hypoxia resulting from primary respiratory failure with damage to the lungs (respiratory hypoxia), violations of structure of hemoglobin of erythrocytes and the associated inability of the latter to transport oxygen (hemic hypoxia), a result of viral myocarditis (circulatory hypoxia) and the fading activity of respiratory enzymes in mitochondria (primary tissue hypoxia).

1. SARS-CoV-2 virus enters cells as a complementary attachment to the receptors of angiotensin-converting enzyme-2 (ACE-2) expressed by lung tissue cells [14, 19, 21, 31].

2. When COVID-19 patients take antihypertensive drugs systematically, the cells of their bodies can increase expression of ACE-2 3–5 times, since antihypertensive drugs block conversion of angiotensin-1 into angiotensin-2 or block angiotensin-2 receptors [14, 15], which promotes penetration of virions into cells, accelerates development of the disease and, quite likely, ultimately makes its course more severe [28].

3. With virions blocking ACE-2 receptors, the normal metabolism of angiotensin-2 (AT-2) is disrupted, which apparently increases AT-2 level locally, inside the lungs, and causes local intrapulmonary vascular hypertension. Further, the blocking probably disrupts the body's arterial regulation system. It is possible that levels of AT-2 expression and virus load make this violation of AT-2 metabolism more pronounced.

4. Vascular hypertension develops as an intrapulmonary symptom against the background of the body's inflammatory response to virus infection; this hypertension leads to the development of pulmonary edema and increased hydration of interstitial tissue, which CT scans visualize as "ground glass opacities". In many COVID-19 patients, respiratory function disruptions and growing hypoxia manifest as a pronounced drop in blood oxygenation. As hypoxia spreads to circulatory, hematic systems and tissue, the body suffers total oxygen deficiency and launches hypoxia mitigation and compensation mechanisms.

B. The first response of the body to acute hypoxia is the genetically determined general adaptation syndrome (GAS), which implies a sharp and significant increase of the cortisol level.

1. Further drop in oxygenation translates into buildup of acute hypoxia and dysfunction of many tissues and organs, including those critical to the body's vital functions [5, 12].

2. The body perceives acute hypoxia as a dangerous violation of homeostasis [10, 11].

3. Same as other life-threatening disorders of homeostasis, acute hypoxia triggers a set of GAS reactions [9, 11] and, consequently, a significant increase of the cortisol level [2, 7].

Nota bene! Currently, there are no routines to control cortisol level in COVID-19 pneumonia patients adopted in clinical practice, therefore there is but a small chance of finding published papers describing hypoxia and cortisol level correlation in COVID-19 patients.

C. Increased level of cortisol significantly changes functioning of the immune system, hematopoiesis, rheological and coagulation properties of blood (maintenance thereof), and disrupts production of eicosanoids [4].

1. The release of cortisol boosts the number of neutrophils [4, 6, 22, 23], which makes them attack not only virions but also pulmonary epithelium, vascular endothelium and other cells. Massive damage to the lung vessels' endothelium cells stimulates formation of parietal blood clots that disrupt hemodynamics, with further development of circulatory hypoxia being the result thereof.

2. The release of cortisol suppresses functional activity of lymphocytes and negatively affects their number [4, 18, 24], which bereaves the immune system of the majority of its antiviral competences that enable selective and targeted response to viral infection (blocking virions from entering cells and their subsequent elimination, as well as selective destruction of infected cells).

Nota bene! The fact that blood plasma transfusions from people that recovered form COVID-19 to current COVID-19 patients in severe conditions proves a very effective therapy (such blood plasma contains antibodies to SARS-CoV-2) highlights the importance of this selective and targeted immune response.

3. The release of cortisol degrades the number of monocyte macrophages, which normally eliminate virions tagged by antibodies [4, 13].

4. The release of cortisol increases the number of erythrocytes and platelets and enhances the vasoconstrictor effect of other hormones [4], which worsens blood fluidity, increases its viscosity and coagulability, thus promoting thrombosis (including disseminated intravascular coagulation). Jointly, these changes further aggravate hypoxia through the development of its circulatory component [13].

5. The release of cortisol suppresses production of the whole range of eicosanoids, including prostacyclins and thromboxanes [4]. In patients whose blood is prone to grow highly viscous and clot (which is typical for patients with increased basal level of cortisol), the disappearance of this pair of "operational control moderators" of rheological properties of blood can lead to thrombosis (including disseminated intravascular coagulation syndrome, acute respiratory distress-syndrome) and significantly boost circulatory hypoxia [13].

6. The release of cortisol, as can be expected, contributes greatly to the development of cytokine storm. Inflammatory cytokines, produced on the mass scale at the initial stage of response to inflammation by mast cells and then by neutrophils, which are abundant in the inflammation zone, should normally trigger activation of the adaptive immunity system (lymphocyte system) and migration of monocyte macrophages to the inflammatory zone. At the final stages of inflammation response, anti-inflammatory factors produced by macrophages (transforming TGF-β growth factor) and partly by lymphocytes [29] block migration of new neutrophils to the inflammation zone and production of inflammatory cytokines by those neutrophiles and mast cells [20, 25, 26]. Against the background of increased basal level of cortisol, when the function of macrophages and lymphocytes is suppressed, inflammatory response cannot complete and inflammation can continue in a self-sustaining mode or develop further, turning into a cytokine storm. Eicosanoid mediators (lipoxins, resolvins, prostaglandin D2, etc.) normally play an equally important role in the completion of inflammatory response [14, 17], but in the considered case their production is also repressed by cortisol [1, 3, 4].

At the end of this sequence of theoretical considerations, we considered it appropriate to present for discussion several generalizations related to the hypothesis, which, in our opinion, are of practical importance.

1. Decreased blood oxygenation and increased cortisol level precede changes in the rheological and coagulation properties of the blood.

If this assumption finds laboratory-backed confirmation in COVID-19 pneumonia patients, the time-conjugated moments of onset of the blood oxygenation level decrease and cortisol level increase should trigger a mandatory blood coagulation properties monitoring routine and an appropriate anticoagulation course.

2. Acute hypoxia developing in COVID-19 pneumonia patients harms those with malfunctioning organs more severely when such malfunctioning is caused by chronic diseases. Organs working at the top of their capabilities will fail in the event of insufficient supply of oxygen, even if its level is extremely low but sufficient to maintain the vitality of the body. Pathological process quickly acquires properties of an avalanche.

3. The search for means and ways to prevent the negative effect cortisol has on the physiological processes in the bodies of severe covid pneumonia patients (and, probably, in cases of pneumonia of different etiologies) can be considered a promising direction of research aimed at increasing the efficacy of treatment of inflammatory lung diseases.

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