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THE ROLE OF BLOOD TRANSPORT PROTEINS IN ADAPTATION REACTIONS TO EXTREMELY UNCOMFORTable CONDITIONS OF THE NORTH AND THE ARCTIC

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The purpose of this review is to integrate data on the role of blood transport proteins in adaptation reactions to extremely uncomforTable conditions of the North and Arctic of the Russian Federation. Regulation of shifts in homeostasis in humans under unfavorable Arctic conditions is carried out, among other things, by increasing the production of haptoglobin and transferrin, which perform antioxidant and immunomodulatory functions. An increase in the concentration of immunoglobulins in the blood ensures the efficiency of utilization of metabolic products, components of cellular destruction and damage. In the unfavorable conditions of the North and the Arctic, a shift and disruption of adaptive changes in lipid metabolism occurs.

Keywords: haptoglobin; transferrin; immunoglobulins; LDL; HDL; adverse conditions of the North and the Arctic; adaptation.

Introduction. The risk of adaptation failure is caused by stress and depletion of the body's functional reserves when exposed to adverse factors. Based on changes in the parameters of the hepatobiliary, immune, antioxidant and lipid transport systems that provide adaptive and compensatory adjustments, an assessment of the state of adaptability is carried out and the risks of disruption of physiological adaptation mechanisms are determined [39].

The influence on the human body of a complex of unfavorable factors in the northern and arctic territories is accompanied by a restructuring of the internal environment of the body and is manifested by changes in the physiological parameters of the blood system. A shift in the parameters of the blood system towards lower or higher values relative to the regional normal limits is a criterion for the risk of failure of adaptation, which in turn is caused by the tension of the immune, metabolic and endocrine regulatory mechanisms [9].

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It has been esTableished that residents of the North experience a predominantly decrease in albumin concentration and a change in the content of other protein fractions, including α2-macroglobulin, ceruplasmin, transferrin, and immunoglobulins [8,41].

The purpose of this review is to integrate data on the role of blood transport proteins in adaptation reactions to uncomforTable and extremely uncomforTable conditions of the North and Arctic of the Russian Federation.

The role of transferrin, haptoglobin, immunoglobulins and lipid transport complexes in adaptation reactions to the conditions of the North and the Arctic. In conditions of high latitudes, the development of hypoxia is due to oxygen deficiency and rarefaction of the air. With the development of a hypoxic state, hypoxia-induced factors (HIFs) are activated. Subsequently, in response to the low oxygen content in the blood, the activation of HIFs increases the transcription of various genes that ensure adaptation to hypoxia at the cellular and systemic levels [23,32].

HIF-1 controls an increase in erythropoietin levels, erythropoietic activity and hemoglobin synthesis. HIF-1 has been shown to regulate the expression of genes involved in iron metabolism: haptoglobin, transferrin, transferrin receptor (TfR). In addition, HIF 1 is involved in the regulation of metabolism and cellular metabolism. Thus, the regulation of HIFs target genes is aimed at ensuring optimal oxygen delivery, regulating metabolism and maintaining cell survival in hypoxic conditions [24,35].

Activation of erythropoiesis in the inhabitants of the North and the Arctic, including due to the effect of low temperatures on the body. During adaptation to cold, along with the intensification of erythropoiesis, an increase in oxygen consumption indicates a metabolic restructuring with the preferred use of lipid oxidation as an energy substrate. Activation of lipid metabolism causes an increase in the oxygen demand of tissues [32].

With an increase in the intensity of erythropoiesis in the conditions of the North and the Arctic, there is a need for binding and transport of free iron by transferrin and heme iron by haptoglobin. An increase in the intensity of erythropoiesis in the inhabitants of the European North and the Arctic is evidenced by an increase in the concentration of transferrin, a membrane and free receptor for transferrin [9,30,37].

The main function of transferrin is the transport of iron and ensuring the effectiveness of erythropoiesis by maintaining the survival, proliferation, and differentiation of erythroid cells [27]. An increase in blood concentrations of transferrin and receptors for this transport protein is associated with an increase in erythrocyte aggregation, with a 1.5-1.7 times higher frequency of cell aggregation in Arctic residents [26].

Intensification of erythropoiesis, an increase in transferrin levels occurs both in residents of high latitudes and highlands. When adapting to low oxygen levels in high-altitude, high-latitude conditions, activation of HIF-1 and an increase in transferrin content is a mechanism of physiological compensation for a decrease in the availability of Fe and O_2. However,

upregulation of transferrin promotes increased thrombosis and platelet aggregation. In residents of the Himalayan highlands, high levels of transferrin in the blood cause hypercoagulation, increasing the level of thrombin and factor XIIa while reducing antithrombin activity [22]. Increased thrombus formation at elevated transferrin concentrations is associated with the severity of COVID-19 disease and the need to sequester released iron when cells are damaged by the viral particle [7].

The increase in transferrin content in the blood is due, among other things, to its role in maintaining immunological reactivity. Transferrin supports cell proliferation by providing immunocompetent cells with the necessary amount of iron. Lymphocytes affected by antigen or mitogen express IL-2 receptors (CD25) and trigger the expression of transferrin receptor (CD71) in a certain cell cycle, which is a sign of lymphocyte activation and proliferation [9].

The main function of haptoglobin is to ensure the binding of free hemoglobin during the destruction of red blood cells in the circulation. The need for hemoglobin binding in the conditions of the North and the Arctic is due to an increase in damage to circulating erythrocytes as a result of activation of lipid peroxidation (POL) of erythrocyte membranes, depletion of antioxidant protection, and a decrease in the energy supply of erythrocytes [14,15,32].

In conditions of hypoxia, activation of lipid peroxidation processes is accompanied by disorganization and damage to the erythrocyte membrane. The integrity of the erythrocyte membrane is a membrane barrier that preserves the intracellular placement of hemoglobin. The destruction of erythrocytes in the bloodstream (intravascular hemolysis) under hypoxia is accompanied by the release of erythrocyte ATP and hemoglobin in the bloodstream. Free hemoglobin undergoes oxidative degradation to heme or irreversibly binds to haptoglobin [12,16].

The entry of haptoglobin into the intravascular space to neutralize free hemoglobin and the rate of excretion of the formed haptoglobin–hemoglobin (Hp–Hb) complex upon binding to the CD163 receptor of macrophages for subsequent heme cleavage depends on the structure and size of molecules of haptoglobin phenotypes: Hp 1-1; Hp 2-1; Hp 2-2. Thus, the size and molecular weight of Hp 1-1 is much smaller, which determines greater mobility when entering the bloodstream. Hp 1-1–Hb complexes are more efficiently absorbed and removed than Hp 2-2–Hb complexes. Thus, Hp 1-1 has great antioxidant and anti-inflammatory properties [36].

Variation in the frequency of haptoglobin types may determine the susceptibility of population groups to certain diseases. For the European population, Hp 2-1 is most common, 2-2 is less common, and Hp 1-1 is the lowest. The Hp1 allele has been studied most fully in the Russian population, which is characterized by a large frequency variation with a latitude variability of 0.17-0.51. Thus, low Hp1 frequencies are typical for the population of the circumpolar zone and the territory of the European North [3].

However, there is inconsistency in the data on the association of diseases with the type of haptoglobin. The relationship between the incidence of stroke in people with diabetes and the type of haptoglobin is ambiguous [20,25]. The study by Eriksson M.I. did not esTableish an association of haptoglobin type with small vessel disease of the brain (SVD), which is contrasted with data on the association of Hp1 type with SVD in type 1 diabetes mellitus [19]. The content of haptoglobin increases in colorectal cancer and gastric cancer [13,18]. It should be noted that for statistically significant results of the relationship of diseases with the type of haptoglobin, it is necessary to take into account that patients are most often burdened with several diseases [36].

During intravascular destruction of red blood cells, the formation of the Hp-Hb complex is aimed at preventing oxidative stress. Compared with systemic circulation, binding of free hemoglobin in the central nervous system occurs to a lesser extent, due to low production of haptoglobin by oligodendrocytes and astrocytes, as well as minimal CD163-mediated clearance of the formed Hp-Hb complexes by microglia. Increased levels of haptoglobin, Hp-Hb in the brain cause faster absorption of iron by the brain parenchyma and macrophages with a decrease in the neuroinflammation cascade [45].

Damage-related proteins (DAMPs), including haptoglobin, capable of initiating an effector immune response, are being considered in order to combat the development of cancer and autoimmune, neurodegenerative diseases. Haptoglobin has been shown to play an important role in the activation of dendritic cells, their expression of specific markers and Th1-associated proinflammatory cytokines. When stimulated by haptoglobin, the migration of dendritic cells to the lymph nodes and interaction with CD4+ and CD8+ lymphocytes leads to the activation of their effector functions [21].

In the process of adaptation to the conditions of the North and the Arctic, prolonged stress on the regulation of immune homeostasis leads to a change in the reactivity of the immune system, causing the risk of disruption of adaptive rearrangements and determining the tendency to transition acute inflammatory processes into chronic ones [9].

To assess the effect of adverse factors, including climatogeographic ones, on immunological reactivity, it is informative to determine the state of cellular and humoral immunity by determining the content of subpopulations of lymphocytes (CD), serum immunoglobulins (IgA, IgM, IgG, IgE), circulating immune complexes (CIC) and cytokines [39].

Clarifying the general patterns of changes in human immunological reactivity in the conditions of the North and the Arctic, determining the reserve and compensatory capabilities of immune homeostasis in specific conditions or in connection with certain factors, makes it possible to identify the risks of disruption of adaptive restructuring with the selection of the most optimal strategies to prevent the transition to a state of pre-disease, chronization of pathological processes and oncogenesis [33].

Thus, in Arctic conditions, when determining the subpopulations of CD10+ and CD71+ lymphocytes, an assessment of the adaptability of the immune system is carried out. In addition, it has been esTableished that increased cell-mediated cytotoxicity of lymphocytes in people living in the Arctic territory is associated with a reduction in the reserve capabilities of the regulation of the immune system with the risk of the formation of functional deficiency of T-lymphocytes, disimmunoglobulinemia, deficiency of phagocytic protection, causing the early development of environmentally dependent immunodeficiency's, tendency to chronic diseases [33,34].

The cell-mediated cytotoxic activity of CD8+, CD16+ lymphocytes are a reserve mechanism of immune defense in case of deficiency of mature CD3+ T-lymphocytes in the extremely unfavorable conditions of the North and the Arctic. However, the increased cytotoxic activity of lymphocytes causes an increase in the content of tissue damage products and cell destruction in the circulation. After the cytolysis reaction by lymphocytes, an increase in the number of antigenic determinants in combination with immunoglobulins indirectly indicates the presence of non-metabolized cell residues [28,42].

Residents of the North and the Arctic

may have different variants of an immune imbalance in the content of immunoglobulins in the blood. Negative shifts on the part of the immune system in adapting to the adverse climatic conditions of the North are a decrease in the blood content of T-lymphocytes (CD3+) and the concentration of IgA. With a deficiency of lymphocytes with a molecule of the associated signal transduction complex – CD3+, there is a decrease in the activity of the humoral response of IgG and IgA or a predominant predominance of IgM content. A decrease in IgA levels, along with high IgM concentrations, occurs when humoral immune defense factors are stressed, including in conditions of contrasting photoperiodic of the Northern and Arctic territories [9].

It has been shown that the depressing effect on humoral immunity also occurs in conditions of hypoxia in the highlands. Thus, in children and young men living near the middle Elbrus mountains (1850 m above sea level), a decrease in IgA and IgM levels was recorded with a return to baseline levels with long-term adaptation. A study of the main immunity indicators of permanent residents of the mountainous regions of the Tien Shan and Eastern Pamirs (2100-2600 m above sea level) revealed a decrease in the synthesis of IgA, IgM and IgG [4,40].

The functional activity of lymphocytes, including antibody-forming cells, is due to their metabolic program and energy supply. In hypoxia, the metabolism and functions of immunocompetent cells are inhibited. When HIF is activated under hypoxic conditions, the energetic reprogramming of B lymphocytes for glycolytic metabolism manifests itself in a deterioration in the production of high-affinity IgG [29,46].

An increase in the concentration of immunoglobulins in the inhabitants of the North and the Arctic suggests their protective and adaptive effect. Under unfavorable climate conditions, the spectrum of antigenic structures significantly increases and expands, causing the activation of antibody production. An increase in the synthesis of immunoglobulins is aimed at maintaining homeostasis of the body in changing conditions of the external and internal environment, providing directed transport of the substance or substrate that caused their formation and immune complexes to places of disposal and clearance [9,42].

In order to provide energy for adaptive and compensatory reactions, metabolic processes are rearranged with activation of lipid metabolism. The assessment of biochemical parameters of lipid metabolism (total cholesterol, triglyceride levels, LDL, HDL, atherogenicity coefficient) complements information about the adaptive capabilities of the body based on the analysis of the metabolic component of the functional reserves of the body. For people living in unfavorable conditions of the North and the Arctic, a change in the lipid transport system is characterized by the formation of dyslipedemia with an increase in the level of total cholesterol, triglyceride levels, LDL and a decrease in HDL. The occurrence of energy imbalance and disruption of metabolic homeostasis when exposed to unfavorable factors on the human body is a manifestation of disadaptation. The indigenous inhabitants of the North, who adhere to a traditional way of life and type of diet, have the most favorable lipid metabolism profiles. Strengthening protein-lipid metabolism and minimizing carbohydrate metabolism contributes to a high degree of adaptation to extreme climatic and geographical factors [5,6,7,17].

Shifts in lipid metabolism indicators reflect the mobilization of energy resources in response to the complex action of adverse factors. When mobilizing the body's reserves, a decrease in HDL levels causes insufficient compensation for dyslipidemia [44]. Thus, residents of the North and the Arctic are characterized by a high risk of developing disorders in lipid metabolism, manifested by a decrease in the anti-atherogenic protection of the body.

The decrease in HDL levels is due to the dysfunction of lipid transport particles, which occurs during the reorganization of lipid components and changes in the proteome during modification or substitution of the main apolipoprotein A-I (ApoA-I). Thus, an increase in the blood content of acute phase proteins (serum amyloid A, haptoglobin, ceruplasmin, fibrinogen, α1-antitrypsin), components of the complement system (C3, C4A, C4B, C9) leads to a competitive substitution of ApoA-I in HDL.

In conditions of high latitudes, human adaptation to adverse conditions is an extremely complex process that requires the restructuring of the body not only to a complex of climatic and geographical factors, but also to the influence of industrial working conditions. Changes in lipid metabolism indicators are informative under various unfavorable working conditions. It was found that workers of a machine–building enterprise with an increased level of vibration and noise have increased levels of atherogenic lipids (total cholesterol, LDL) and decreased levels of antiatherogenic HDL, which is associated with stress of the functional state of the body. At an oil refinery, workers exposed to the chemical factor showed an increase in concentrations of total cholesterol, LDL with a lower level of HDL. When exposed to electromagnetic fields of industrial frequency, employees were found to have an increase in the level of total cholesterol, LDL, and atherogenic index [11,31,43].

The changes and information content of hematological, biochemical, immunological parameters are shown when the body is exposed to various unfavorable factors, including climatic and geographical factors [1,2,8,10,38,41,47].

Conclusion. So, the effect of the complex of unfavorable climatic conditions of the northern and Arctic territories causes a sufficiently high voltage regulation of metabolic processes, creating a significant need for transportation with the accumulation of metabolic products in the blood, endogenous metabolites [9].

Insufficient utilization and excretion of various waste products from the body is an unfavorable factor. The need for binding and transport for subsequent clearance is due to the accumulation of non-utilized components of cellular damage, destruction with excessive cytotoxic activity of lymphocytes with an increase in blood concentrations of circulating immune complexes.

The change in the content of the components of the blood proteome is aimed at maintaining the optimal functional state of the body under specific conditions. The level of blood proteins must be considered in conjunction with immunological parameters to analyze the direction of changes in metabolism, homeostasis and determine the risk of adaptation failure.

In unfavorable, extremely unfavorable conditions of the North and the Arctic, there are risks of disruption of adaptation against the background of impaired effectiveness of clearance and utilization mechanisms through phagocytosis. Under these conditions, the need for transport proteins increases, ensuring effective binding, transport and utilization of various waste products, including transferrin, haptoglobin, immunoglobulins and HDL.

Thus, the determination of blood protein content is informative in assessing the adaptive capabilities of the body. A change in the proteome displays information about changes in the human body under the influence of adverse factors, including climatogeographic factors. The relationship of blood transport proteins is important for characterizing the state of the body and evaluating the intersystem,

intersystem relationship in the adaptation process.

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