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Metabolism and Physiological Functions Adjustment of the Organism under Stress Influence

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Abstract

Stress reaction of the organism is a process occurring at the cellular, tissue and systemic levels. The organism responds to any adverse effect with a multi-level reaction, which causes the development of stress and, as a result, adaptation. The damaging effect is due to the excessive strengthening of another adaptive effect – lipotropic, that increases the activity of phospholipases and the intensity of free radical oxidation of lipids through the catecholamines and protein kinases. The changes in the immune system during the adaptation stage are to maintain antigenic homeostasis of the internal environment of the organism due to lymphoid cells, lymphocytes and cytokines. Almost all cells with antigen representation function are capable to produce interleukins under certain conditions. The vascular system is a kind of an indicator of any pathological process, determining the state of regulatory and adaptive mechanisms, the features of the connective tissue matrix. Stress causes a restructuring of metabolism and physiological functions, which increases the organism's resistance to acute death. Thus, the physiological meaning of the stress reaction is the emergency mobilization of energy and structural resources of the organism and the creation of positive background for the implementation of reactions, aimed at maintaining homeostasis in extreme situations.

Key words: stress, lipid peroxidation, immune system, blood vessels

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Перестройка метаболизма и физиологических функций организма под воздействием стресса

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Резюме

Стрессорная реакция организма представляет собой процессы, происходящие на клеточном, тканевом и системном уровнях. Организм на любое неблагоприятное воздействие отвечает многоуровневой реакцией, которая обуславливает развитие стресса, и, как следствие, адаптацию. Повреждающий эффект связан с чрезмерным усилением другого адаптивного эффекта – липотропного, который через катехоламины, протеинкиназы усиливает активность фосфолипаз и увеличивает интенсивность свободнорадикального окисления липидов. В иммунной системе изменения на стадии адаптации заключаются в поддержании антигенного гомеостаза внутренней среды организма за счёт лимфоидных клеток, лимфоцитов, цитокинов. Практически все клетки, при определённых условиях осуществляющие представление антигена, способны к продукции интерлейкина. Сосудистая система является своеобразным индикатором любого патологического процесса, определяя состояния регуляторных и адаптивных механизмов, особенности соединительнотканного матрикса. Стресс вызывает такую перестройку метаболизма и физиологических функций, которая повышает устойчивость организма к острой гибели. Таким образом, физиологический смысл стресс-реакции заключается в экстренной мобилизации энергетических и структурных ресурсов организма и создании положительного фона для осуществления реакций, направленных на поддержание гомеостаза в экстремальных ситуациях.

Ключевые слова: стресс, перекисное окисление липидов, иммунная система, сосуды

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ORGANISM STRESS REACTION

Environment influences all living organisms in modern society. Organism response to a non-specific stimulus first appeared in the Selye works at the beginning of the last century and were considered as a General adaptation syndrome. It was only in 1946 that Selye began to systematically use the term "stress" for the notion of 'general adaptation tension'. Stress reaction of the organism is a process, occurring at the cellular, tissue and systemic levels [21, 25]. Stress reactions during its development pass three stages: the alarm stage, the resistance stage, the exhaustion stage [10].

The alarm stage occurs in reply to the direct action of the stressor (6–48 hours). During the alarm stage the functional activity of organs and cells, that are responsible for the life-supporting reserve of the body, increases. Selye distinguished two phases of the alarm stage: the shock phase and the anti-shock phase. In the shock phase, we can observe hypotension, muscles hypotonia, disorders of the permeability of the vascular and capillary membrane, exudation, haemoconcentration, general catabolism, gastrointestinal ulcers, leukocytosis, then acute leukopenia (eosinopenia). In the anti-shock phase, protective mechanisms develop: we see increase in the secretory activity of the cortex and medulla of adrenal glands, increase in the secretion of adrenaline, adrenocorticotrophic hormone (ACTH), glycine cleavage system (GCS). There is involution of the thymic-lymphatic system. If the stressor continues to act further or its effect was strong, the second stage comes – an increase of resistance. Generally, 48 hours after the exposure, we can observe adrenal hypertrophy, an increase of adenohypophysis basophilic cells, thyroid hyperemia, and eosinophilia. Resistance to the stressors increases. Selye interpreted stress that reached the resistance stage as a 'general adaptation syndrome'. Then, morphology and functioning of organs and tissues restore. If the stress factor is destructive, the body resistance is reduced, and the third stage of exhaustion comes. This stage can lead to death. But the organism has a clear adaptive orientation, which is a result of self-preservation. This process is based on activation of the glucocorticoids and catecholamines synthesis, which contribute to the activation of organs and systems, responsible for adaptation. The damage effect has the relation with the excessive strengthening of another adaptive effect – lipotropic. This effect increases the activity of phospholipases and the intensity of free radical oxidation of lipids through catecholamines, protein kinases [8, 12].

The changes in the immune system during the adaptation stage are to maintain antigenic homeostasis of the internal environment of the organism due to lymphoid cells, lymphocytes, and cytokines. Almost all cells with antigen-presenting function are capable to produce the interleukins under certain conditions.

VASCULAR SYSTEM REACTION TO THE DAMAGING FACTOR

The vascular system is a kind of an indicator of any pathological process. It determines the state of regulatory and adaptive mechanisms and the connective tissue matrix features [19]. Connective tissue consists of a complex

of cells, fibers and the basic substance. They have similar origin and functions. Connective tissue can be found everywhere in the entire organism. Collagen and elastic fibers are the fibrous structures of connective tissue. The predominant cell elements are fibroblastic cells [20]. Fibroblasts form collagen, elastin, proteoglycans and glycoproteins. Fibroblasts maintain the extracellular matrix and destroy the extracellular matrix in terms of remodeling the skeleton fibers. The source of fibroblasts are low differentiated cells of connective tissue of mesenchyme origin and bone marrow predecessors. The number of fibroblasts increases under the influence of cytokines and chemokines, as well as during the development of inflammation and fibrosis. They actively leave the bloodstream and participate in remodeling and repairing of connective tissue [13, 22, 32, 35]. Progenitor cells of the fibroblastic row can be differentiated into myofibroblasts and adipocytes, chondrocytes and osteoblasts [16].

Immobilization of animals leads to the development of general stress, which is based on activation of stress-realizing systems (corticotropin-releasing factors, adrenocorticotrophic hormone, glucocorticoids and catecholamines). Catecholamines and glucocorticosteroids are powerful vasoconstrictors. There is a narrowing of the vessels, the total peripheral resistance increases with their long-term and excessive blood flow. It leads to disruption of organs and tissues hemodynamics [6]. Most authors believe that imbalance, occurring in the sympathetic and parasympathetic parts of the autonomic nervous system, precedes hemodynamic disorders and, consequently, is the earliest premonitory sign. At extreme conditions, hemoreological changes are observed, which acquire a certain degree of severity from the duration of exposure. The changes in hemoreological properties of blood lead to hemodynamics and microcirculation disorders [4].

A significant amount of scientific works on experimental models prove that oxidative stress, in which a large number of oxygen active forms (free radical compounds) is accumulated in the blood, stimulates considerably the progression of endothelial dysfunction. The effect of stress is an important factor in the development of vascular remodeling through endothelial dysfunction. With excessive activation of oxidative stress, the cell wall alters, which leads to excessive macro-vascular permeability. An experimental study of the balance of pro- and antioxidant system showed that long-term oxygen intoxication leads to violations of ion transport and physicochemical properties of membrane proteins and lipids, which leads to changes in the activity of membrane-bound enzymes, reduction of the electrical stability of their lipid layer.

A number of authors have noted changes in the values of the linear blood flow speed, an increase in the average linear systolic and linear diastolic blood flow speed, and pressure gradient during acute immobilization stress [5].

According to literature sources, the indicator parameter of the response to stress is the reaction of electrophoretic mobility and erythrocytes [39]. The hormones are released under the stress: catecholamines, glucocorticoids, etc. That leads to the implementation of lipase and phospholipase activation, to an increase of the free radical oxidation of lipids [24, 33, 37].

LIPID PEROXIDATION AND STRESS REACTION

In response to stress factors, the organism reacts by the intensification of free-radical oxidation, which is realized by the mechanisms of lipid peroxidation [30, 36]. With excessive activity of oxidative stress, the cell walls are altered, leading to the increase of macro-vascular permeability. As we have already mentioned, an experimental study of the balance of pro- and antioxidant system revealed that long-term oxygen intoxication leads to violations of ion transport and physico-chemical properties of membrane proteins and lipids, leading to changes in the activity of membrane-bound enzymes, reduction of electrical stability of their lipid layer. During the experiment, A.V. Deryugina concludes that the phase change of erythrocytes is associated with the action of stress-realizing components. Along with this, the concentration of malondialdehyde (MDA) and glutathione increases. The researchers assumed that the concentration of MDA in erythrocytes is determined by an increase in the content of adrenaline in the peripheral blood. The decrease of the MDA concentration may be due to the effect of corticosteroids concentration that appears during of the stress-reaction realization. Corticosteroids activate compensatory-adaptive reactions in the erythrocytes, thus increasing the content of glutathione. Glutathione and glutathione-dependent enzymes contribute to adaptation to oxidative stress [3].

There are pathological changes due to free radical oxidation of biomolecules by active oxygen forms under various types of stress (immobilization, pain, cold, acoustics) [28, 29]. Thus, the proteins of the plasma membranes are primarily subjected to change, that lead to the depolymerization of the membranes and cell lysis. Stress leads to general adaptation syndrome, the main role in which is given to the autonomic nervous system. Adrenaline and norepinephrine are neurotransmitters of the sympathetic nervous system. They are actively involved in system changes of the lipid peroxidation under stress [7, 14]. Intensification of free radical oxidation was confirmed to cause development of secondary changes in organs and tissues at stress [24, 27].

Under the emotional-pain stress, protein peroxidation increased by 26.7 % in blood plasma and liver of rats, by 8.4 % – in the lungs and by 9.1 % – in the myocardium. Under the preventive introduction of alpha tocopherol, the level of protein peroxidation significantly decreased, that indicated pronounced stress-protective effect of antioxidants.

Tension and depletion of antioxidant system (AOS) were observed during cold exposure of rats, as evidenced by a significant decrease in the level of ceruloplasmin in the blood of the experimental animals, as well as a decrease in vitamin E and reduction of catalase and superoxide dismutase (SOD) activity, compared with the same indicators in the intact group. The reaction of quantitative and qualitative changes in the composition of blood cells is noted during study of the stress response. It can reveal compensatory mechanisms of organism adaptation to stress. Immobilization disturbed blood redox balance. Measurement of the MDA level, characterizing the lipid peroxidation of erythrocyte membranes, showed 7 % increase, compared with the control after one hour

of immobilization. The activity of SOD and catalase increased by 13.4 % and 9.7 % respectively [9]. The model of emotional-pain stress shows that free radical oxidation of lipids (hydroperoxides of phospholipids, Schiff bases) increases 2–3 times depending on the stress duration.

AOS is represented by at least three levels of protection. The first level is realized in the form of mitochondrial respiration. The second level (anti-radical) is intended to inhibit free radical processes of the lipid peroxidation system. At the third level (anti-peroxide), the formed peroxides are destroyed. SOD, catalase and peroxidase are antioxidant enzymes that act at all levels. If the first line of defense suffered hyperoxia rise, as a result of weak splitting of O₂, which leads to failure of mitochondrial respiration, and, as a consequence, the emergence of oxygenic stress. Some destabilizing processes in cell violate the second and third levels of protection, so their impact on free radicals and peroxides changes.

The decrease of the lipid peroxidation intensity in blood plasma due to the increase of the activity of antioxidant enzymes – superoxide dismutase and catalase, glutathione reductase – is observed in short-term immobilization stress. The increase of the antioxidant system activity at response to the intensification of free radical oxidation processes due to the depletion of antioxidant enzyme systems resources leads to its oppression [15, 31]. Apparently, the deficiency of antioxidant protection is not characteristic of stress itself, but of later and more severe phenomenon of tissue damage [17, 34, 38]. This function leads to damage of the membranes during prolonged or intense stress reaction. It is transformed from an adaptive effect into a damaging one. Under stress, the system of lipid peroxidation changes. This change is associated both with these products' increase and decrease. The same change occurs in the system of AOS, which suppresses the activity of lipid peroxidation [2, 26]. Due to the resources depletion of antioxidant enzyme systems, it leads to antioxidant protection system oppression. This function is not typical for the stress itself, but for the later and more severe phenomenon of tissue damage. As a result of the accumulation of lipid peroxidation products, cell membranes are destroyed and vascular permeability is disturbed [11, 18].

IMMUNE RESPONSE TO STRESS

Inhibition of the immune system function under stress is associated with the suppression of T-system, changes in the number of recirculating T-cells in relation to B-cells and macrophages [23].

The mechanism of the changes of immunoreactivity during stress is associated with activation of the mediators of the stress system – corticotropin-releasing hormone, adrenocorticotrophic hormone, glucocorticoids and catecholamines. The blood system is mobilized and the immune response is activated under the moderate increase of the mediator's secretion. With increased secretion of these mediators, immunoreactivity is suppressed. Immunosuppression under the stress is associated with an increase of the glucocorticoid hormones concentration in the blood serum, redistribution of erythrocytes and activation of T-suppressors. Stimulation of immunity in the form of lymphocyte mobilization, interaction with he-

matopoietic stem cells of the bone marrow is an adaptive reaction, as a result of which there is a period of recovery or with prolonged exposure to stress a state of secondary immunological failure develops.

There are three types of stressors: acute stress factors, short-term stressors and long-term stressors. The immune response depends on the duration of stress exposure. In acute stress, there is an increase in the number of circulating suppressors/cytotoxic T-cells, but long-term stress factors reduce their number.

Acute stress can enhance the immune function of the adaptive response, but chronic stress suppresses the immune response due to the depletion of the organism resources. The secretion of adaptive "stress" hormones (catecholamines, vasopressin, etc.) leads to an increase of the calcium entry into the cell, mobilization and reduction of glycogen reserve and to the implementation of the lipid triad. The lipid triad is the activation of lipase, phospholipase and the increase in free radical oxidation of lipids. As a result of the lipotropic effect of the stress reaction, a modification of the lipid bilayer of the membranes occurs, the viscosity decreases and the membrane fluidity increases.

The complex effect of stress hormones to the immune system can cause quite pronounced secondary immunodeficiency, especially during prolonged stress exposure. Selye assumed that chronic stress should be regarded as an oncological risk factor. Catecholamines promote the production of erythropoietin and through it – the activation of erythropoiesis. Erythropoiesis and thrombocytopoiesis are further amplified under the influence of glucocorticoids and androgens secreted in some individuals under the stress. A number of stressors greatly stimulates the vasopressin genes. Vasopressin in high concentrations increases the production and thrombogenic functions of platelets, as this inhibits the synthesis of plasminogen activators and the development of coagulation factors in the liver, which involves glucocorticoids. As a result, stress leads to increased coagulability and thrombogenic potential of blood, erythropoiesis and thrombocytopoiesis [10].

During acute immobilization stress there are changes in the pituitary, adrenal, thyroid glands. The conducted research [1] confirms that the state of prolonged stress leads to the same changes.

In the central nervous system and visceral organs, the disorders of all components of microcirculation are revealed. They arose during a single immobilization and progress during the prolonged stress. In the heart and lungs the disturbances of intravascular microcirculation component are marked, which are morphologically manifested in the form of sludge phenomenon and separation of blood and leukostasis in the vessels of the stomach wall. The change of vascular tonus and blood filling of organs is revealed, the phenomenon of ischemia in many organs is noted, which is a violation of the vascular component of microcirculation, an increase in the permeability of blood vessels and the integrity of microvessels. These manifestations are most pronounced in animals under prolonged stress, and in a number of organs (heart, lungs, liver, kidneys, stomach) microcirculatory disorders lead to the development of dystrophic and necrotic changes. The separation of the blood to plasma and structural elements

is manifested, there is a sludge phenomenon associated with increased adhesion, agglutination and aggregation. Damage of the vascular endothelium and exposure of the subendothelial layers triggers the platelet reaction, blood coagulation and causes vasospasm. The changes in local blood flow of the endocrine glands are noted, and it is manifested as a functional hyperemia. Thus, it indicates a significant activation of the main stress-releasing systems.

Stress causes such restructuring of metabolism and physiological functions that increases resistance of the organism to acute death. Thus, the physiological meaning of stress-reaction is the emergency mobilization of energy and structural resources of the organism and the creation of a positive basis for the implementation of reactions aimed at supporting of homeostasis in extreme situations.

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