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BIOLOGICAL ACTIVITIES THE VALUE OF INTERLEUKINS IN THE HUMAN BODY

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Abstract. The basic effects of proinflammatory interleukin-1 and anti-inflammatory interleukin-10 focus of on the cells of inflammationa have been presented. These interleukins are key regulatos of cytokines in the inflammatory process. According to the analysis of research, both deficiency and excess of secretion of these cytokines in peripheral blood and brain structures, the organism of humans and animals at the early stages of ontogenesis determines its further cognitive, emotional development and the risk of developing pathology of the central nervous system in the perinatal, postnatal period, in adolescence and adulthood. Possibility of adaptive role of pro- and anti-inflammatory cytokines on the example of interleukin-1 and interleukin-10 as in the formation of bioelectric activity of the human brain during the adolescent period of its development, and in general throughout his life to maintain the body's homeostasis in an uncomfortable environment.

Keywords: cytokines, interleukin, interleukin-1 interleukin-10, central nervous system, inflammation, regulation.

Introduction. Cytokines are a group of polypeptide mediators involved in the formation and regulation of the body's defense reactions [1]. Biological effects of cytokines are mediated through specific cellular receptor complexes that bind cytokines with very high affinity, and individual cytokines can use common receptor subunits [14].

Depending on the nature of the effect on the inflammatory process, cytokines are subdivided into pro-inflammatory, involved in the initiation of inflammation, and anti-inflammatory [2]. The key pro-inflammatory cytokine is interleukin-1 (IL-1) [7], the main anti-inflammatory is interleukin-10 (IL-10) [16]. IL-1 is subdivided into 2 fractions - IL-1α and IL-1β, that having the same molecular weight of 17.5 kDa [12]. Both cytokines are encoded by different genes, but have a homology in the amino acid sequence of 26%, have almost the same spectrum biological activity and compete for binding with the same receptors. In addition, a third protein with a similar structure has been discovered. The ability to specifically bind to IL-1 receptors without manifesting biological activity.

Competing with IL-1 for the same receptor, it blocks the biological activity of IL-1 and, due to the presence of similar properties, it was named "receptor antagonist of IL-1"(RAIL) [10, 13]. IL-1 is produced by many cells in the body. Its main

sources in the body are monocytes and macrophages [13], as well as Langerhans cells, kupffer's cells in the liver, endothelial cells, fibroblasts, keratinocytes, microglia cells, natural killer cells, neutrophils, T-lymphocytes, except for T-helpers, dendritic cells, etc. [1, 9, 10]. The induction of IL-1 synthesis can be caused by the whole a number of biologically active substances, the main ones which are components of bacterial cell walls (lipopolysaccharides and peptidoglycans) [13], and also antigens, immune complexes, cytokines, cellular degradation products [15].

In humans, IL-1β is the main form of secretory IL-1 into the environment, which is explained by the predominant finding of IL-1α in the form of a membrane form [13]. Currently, the enzyme IL-1-convertase has been discovered, which converts the precursor of IL-1β into a mature biologically active form by cleaving the polypeptide chain of the molecule between amino acid residues of asparagine and alanine [3].

This enzyme is found in macrophages and macrophage-like cells. It is specific only for IL-1β and does not affect the IL-1α precursor. All known biological effects of IL-1 are carried out through its binding to specific membrane receptors expressed on various types of target cells. It is known, three types of IL-1 receptors, designated receptors IL-1 types I and II, and an accessory protein of the IL-1 receptor. All three receptor proteins are expressed by cells constitutively, but their number may increase under influence of a number of bacterial inducers, cytokines, hormones and other biologically active substances. Type I IL-1 receptors are found on T cells, keratinocytes, chondrocytes, hepatocytes, fibroblasts, endothelial and synovial cells [10, 13] and are used for signal transmission. Type II IL-1 receptor present on B-lymphocytes, neutrophils, cells bone marrow, macrophages [17]. Type II receptors exist exclusively for binding IL-1.

The biological action of IL-1 can only be blocked by monoclonal antibodies to the receptor Type I, but not type II receptor antibodies. Obviously type II receptor serves to block biological effects associated with overproduction of IL-1, because of such properties, the type II IL-1 receptor is called the "trap receptor". It has been shown that on some types of cells, in particular on B-lymphocytes, they can both I and II receptors are simultaneously expressed type. The role of "accessory protein" is determined by maintaining the conformation of the receptor-ligand complex.

For IL-1, it is characteristic that the response of cells to its action develops in the presence of a minimum number of occupied specific receptors and extremely low concentrations of the ligand. The pleiotropic type of biological action of IL-1 is manifested starting from the molecular intracellular level. Even though the minimum number of expressed receptors and disappearing picomolar concentrations of IL-1 itself, a cellular response is triggered, which ultimately leads to gene expression of about 100 cytokines, hormones, enzymes, growth factors, other biologically active substances and their receptors. Therefore, all the numerous biological effects of IL-1 in the body are determined already at the subcellular level. Target cells for IL-1 are T- and B-lymphocytes, macrophages, neutrophils, endothelial cells, dendritic cells, basophils, fibroblasts, osteoclasts, hepatocytes and other cells, i.e. targets are cells of almost all organs and tissues [13].

The action of IL-1 on hepatocytes leads to a decrease in albumin synthesis and increased protein production "Acute phase". Apparently, in order to provide the required amount of amino acids for the synthesis of these proteins, catabolism occurs under the influence of IL-1, proteins of muscle tissue [8, 10]. IL-1 affects cells myeloid row, while erythropoiesis is inhibited [10]. An integral part of the biological action of IL-1 is its stimulating effect on connective tissue metabolism. It stimulates the proliferation of fibroblasts and increases their production prostaglandins, growth factors and a number of cytokines.

Under the influence of IL-1, connective tissue cells increase the synthesis of collagen, collagenase, and other enzymes. However, the result of the repair may be hypertrophic or keloid scars, that associated with increased formation of granulation tissue, is enhanced under the influence of high concentrations of IL-1 [5]. For some cells, it is a chemoattractant [7]. IL-1 promotes the release biogenic amines from basophils, mast cells, causes maturation and proliferation of B-lymphocytes [1]. Under its action marked inhibition of lipase, leading to an increase in the blood pool of triacylglycerol, in bone, cartilaginous and muscle tissues induction synthesis of proteinases, which causes bone resorption and cartilage and myomalacia [6]. IL-1 can indirectly induce hyperalgesia through stimulation of synthesis prostaglandins and thromboxanes, modulation of sympathetic fibers through increased expression of receptors for nerve growth factor and bradykinin [4, 22]. IL-1 participates in the regulation of the functions of the endothelium and the system blood coagulation, inducing procoagulant activity, synthesis of proinflammatory cytokines and expression of adhesion molecules on the endothelial surface [13] and also acts on the vessels, causing vasodilation [10]. An oxygen explosion is observed in neutrophils under the influence of IL-1 [6]. One of the most important biological effects of IL-1 is the activation lymphocytes and especially the activation of T-helpers [10].

The systemic influence of IL-1 is manifested indirectly on hypothalamus through the synthesis of prostaglandin E2, which is accompanied by hyperthermia and the production of pituitary releasing factors [6].

IL-10 is an inhibitor of inflammation and the cytokine cascade [16]. It inhibits the synthesis of cytokines T-helpers 1 (Tx1) [9], chemokines, adhesion molecules [6], inhibits the synthesis of monocyte / macrophage tumor necrosis factor α (TNFα), IL-1, interleukin-6 (IL-6), interleukin-12 (IL-12), granulocyte colony-stimulating factor (G-CSF), etc. [7]. This neurotransmitter suppresses effector functions macrophages, T cells, natural killer cells, neutrophils [16, 21, 25], synthesis of interferon γ (IFN γ), is a co-stimulator of proliferation and maturation thymocytes, chemotaxis. IL-10 enhances the growth of obese cells, B-cell proliferation and secretion of immunoglobulins [9]. In experimental models, IL10 showed an analgesic effect [4]. IL-10 is protective for the vascular endothelium, because it weakens the effects of angiotensin II, activated by the products of oxidative stress [8], and restores the activity of nitric oxide synthase, suppressed by inducers of endothelial dysfunction [2,3]. The main function of the IL-10 is limitation and relief of the inflammatory process.

Signals from cytokines can also affect on the central nervous system (CNS) and without involvement of the brain parenchyma for example, with an indirect increase in the secretion of corticosterone due to systemic administration cytokines [5]. There is a known way of activating cytokines in the brain through the introduction of an antigen along the olfactory nerves, bypassing the bloodstream, with neurodegenerative diseases [4], by the neuro-conductive route through the vagus nerve system [3], as well as through the bloodstream of the mucosa shell of the nose. It is also shown that the introduced intranasally IL-6 promotes better preservation of emotional and procedural memories during sleep, is given cytokine optimizes the consolidation of emotional memory [6].

By the penetration of cytokines into tissues the brain is also the lymphatic system the brain, due to which, through the lymphatic vessels of the neck, immune factors from peripheral tissues can enter the brain [7]. IL-10 is an anti-inflammatory cytokine that is produced in humans by activated T-lymphocytes (clones Th0, Th1 and Th2), T-lymphocytes, activated B-lymphocytes, cells B-cell lymphomas, mast cells, lipopolysaccharide-activated monocytes and macrophages [1]. IL-10 is able to suppress the production of proinflammatory cytokines, interferon, proliferative response of T cells to antigens and mitogens, as well as secretion by activated monocytes interleukin-1-beta, tumor necrosis factor alpha (TNF-alpha) and IL-6 [8]. However, IL-10 under certain conditions can stimulate the synthesis of immunoglobulins, activate T cells with cytotoxic action. This means that the IL-10 cannot fully consider an immunosuppressive cytokine [1].

Cytokines have a significant effect on the formation of mechanisms of neuroplasticity and stress reactivity in early life stages underlying human cognitive development and adaptation to the environment in subsequent stages in life. It is believed that the development of the body, a child in conditions close to sterility, forms an inadequate immune response to environmental factors in the adult period, for example, in the form of bronchial asthma and other types of allergies. Formation of "lean phenotype" in the form of overweight and metabolic disorders in people born with severe underweight, also associated with impaired neuroimmune relationships in the early stages of ontogenesis [12]. In the offspring of rats receiving Bendotoxin during pregnancy, in the postnatal period, a decrease in the number of dopaminergic neurons in the nigrostrial system of the brain and changes in the motor activity [10], increased preference to alcohol consumption [13].

In a study by F.M. Sonmez et al. [28] demonstrated the ability of antiepileptic drugs to reduce the level of immunoglobulins in the blood serum and affect production and level of certain cytokines. It has been shown that the use of valproic acid and topiramate in prepubertal children period with idiopathic generalized and partial epilepsy helps to reduce their initially high level of IL-10 with minimal change in pro-inflammatory cytokines.

There is enough information about the role of cytokines in the formation of the nervous system at the early stages of ontogenesis, including at the prenatal stage,that is obtained in an experiment on animals. The fact of the long-term effect of the

imbalance of pro- and anti-inflammatory cytokines, formed in the early stages of ontogenesis, on the functioning of the central nervous system organism in children, adolescents and mature age. The role of cytokines in the development of brain bioelectrogenesis in persons during the period puberty, especially in neurologically healthy people, is not adequately covered systematically and needs further attention from researchers. A promising direction may be the continuation of the development of environmental neuroimmunology, in which the role of cytokines in the age-related formation of neurophysiological mechanisms of regulation of the body a person in an uncomfortable environment habitat requires further study and reflection. The study of the role of cytokines in relation to the peculiarities of the psycho-neurophysiological status of northerners will make it possible to expand ideas about the immunological mechanisms

In conclusion, having a pleiotropic characterbiological activity, IL-1 regulates all aspects of the inflammatory response and immune response. IL-10 is the most important anti-inflammatory cytokine, which mainly provides anti-inflammatory and anti-cytokine action. Sources of IL-10 are T-helper-2 lymphocytes (Th2)], B-lymphocytes, monocytes / macrophages, keratinocytes, mast cells, thymocytes, a subpopulation of T-lymphocytes with suppressor activity-Tregulators1. Macrophages produce IL-10 under the influence of exogenous and endogenous factors, such as endotoxins, catecholamines, etc. IL-10 circulates as a homodimer consisting of two densely packed 160 amino acid proteins. This cytokine realizes its effects through a receptor complex that is expressed on the surface of many cells. Receptor for IL-10 is high affinity, has a molecular weight of 110 kDa. Target cells for IL-10 are mast cells, B-lymphocytes, neutrophils, natural killer cells, monocytes / macrophages, but the main targets for it are antigen-presenting cells and lymphocytes.

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