MODERN METHODS OF STUDYING THE IMMUNOLOGICAL PROPERTIES OF THE IMMUNOCOMPETENT SYSTEM BASED ON THE INFLUENCE OF MICROBIOLOGICAL FACTORS.

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Abstract. The immune system of humans and animals is one of the most reactive systems of the body, reacting quickly to the effects of damaging factors at the earliest stages. The immune system is formed by a complex of organs and tissues that create protection against foreign endo- and exogenous influences. It arose in the early stages of evolution and its activity is based on the recognition of foreign antigens, their destruction and removal, which is absolutely necessary for the survival of the organism.

Keywords: immunogenesis, lymphoid follicles, reticuloendothelial complex, the thymic stroma.

At present, convincing data have been accumulated indicating that the immune system largely determines the body's resistance to the effects of chemical factors. The central organs of immunogenesis in mammals are the thymus, where the formation and reproduction of T-lymphocytes occurs, as well as the red bone marrow, where B-lymphocytes are formed and multiplied. Peripheral lymphoid organs are lymph nodes, spleen, tonsils, intestinal lymphoid follicles [2].

Lymphoid tissue, being the main development of specific immunological reactions, contains numerous cell populations involved in ensuring the genetic constancy of the internal environment of the body [11]. In this case, the thymus is considered as an immune organ, in which acquired and natural immunity is formed with the help of biologically active peptides [1]. The history of the study of the structural organization and functions of the thymus (thymus, lymphatic, thymus, large retrosternal node) goes back many decades [8, 16]. In the structure of the immune system, the thymus provides the maturation and differentiation of T-lymphocytes, including in the peripheral immune organs, stimulates the integration of various populations of T-lymphocytes and macrophages for the implementation of immune responses.
Until the end of the 20th century, the theory of involution of the thymus of humans and animals was considered indisputable. According to the theory of thymus involution in adolescents 14-15 years old and animals aged 8-9 months. upon reaching the period of puberty, the organ under study undergoes complete involution in the body and loses its functional purpose. The founders of this theory believed that the thymus reaches its maximum functional development in newborns. However, there are substantiations for the morphofunctional significance of this gland in northern animals throughout all periods of individual development and age-related changes in the organ until biological death occurs. In a 4-week-old embryo, the reticuloendothelial complex and its cellular elements are formed. The thymus is a combination of epithelial and mesenchymal reticules and together with the capillary network form a reticulo-endothelial complex. Epithelioreticulocytes are differentiated and different generations of thymocytes appear. It has been proven that thymus T-lymphocytes regulate cellular immunity in the body and form thymus-dependent organs (spleen, lymph nodes, etc.). The epithelial islets of the thymus of young adult animals secrete into the blood a secret that contains hormones of the thymositis family. These hormones regulate humoral immunity in the body of animals and humans [9]. The development of T-lymphocytes is the result of the interaction of progenitor cells and immature thymocytes with components of the thymic stroma, which contains several types of cells that create a supporting frame and form a microcircle for developing thymocytes [16].

As a result of immunohistochemical studies [17], the presence of serotonin was found in the precursors of T-lymphocytes (CD4-CD8-), in immature cortical cells (CD4 + CD8), in mature medullary cells (CD4 + CD8-), as well as in epithelial cells forming Gassal's little bodies. Autopsy studies of the thymus of people of different age groups made it possible to verify the expression of serotonin in human thymus cells at all stages of ontogenesis. A significant increase in the number of cells containing serotonin in elderly people and the preservation of this hormone in elderly people and long-livers at the same level as at the initial stages of ontogenesis was established. The intensity of serotonin synthesis does not change during ontogenesis. The data obtained convincingly indicate the preservation of the endocrine function of the gland during aging [17].

The regenerative potential of the thymus was investigated in adults (54 people) who underwent chemotherapy for 12 months for lymphoma. The dynamics of thymic activity was analyzed by assessing structural changes in the thymus using sequential computed tomography, correlating them with the results of studying the thymus by simultaneous analysis of T-cell receptor excision circles
(sjTREC) and CD3i (+) recently emigrated from the thymus (recent thymic emigrants - RTE) in the peripheral blood. In addition, the regeneration processes in the thymus were assessed based on the recovery of peripheral CD4 (+) T-cell lymphocytes after chemotherapy. An increase in the investigated organ after chemotherapy in comparison with the initial level, called recurrent thymic hyperplasia, was detected in 20 patients aged 18-53 years (average 33 years). Using general linear models of mathematical analysis, it was found that patients with hyperplasia had a faster recovery of sjTREC and CD3i (+) RTE levels after chemotherapy than in patients of the same age, gender, diagnosis, stage diseases, thymus function at baseline, but without hyperplasia. These data indicate that the adult thymus retains the ability to regenerate after chemotherapy, especially in young people. The presence of hyperplasia can promote the renewal of thymopoiesis and the replenishment of the peripheral CD4 (+) pool of T cells after chemotherapy in adults [10].

The main function of the thymus is to promote the development of T-lymphocytes. The role of cytokines produced in the thymus is mainly to maintain the main processes in the thymus, that is, T-lymphopoiesis. Cytokines also coordinate intercellular relationships. It was found that the main role in the formation of T cells belongs to IL-7, produced by thymic epithelial cells. This process also involves the products of the cell stroma (SCF - stem cell factor, cytokines of the IL-6, IL-15 family, proinflammatory cytokines), or the thymocytes themselves (cytokines acting through y (c) -containing receptors - IL-4, IL-2, IL-9) [5].

The effects of various immunomodulators on the immune system have been studied. Polyoxidonium, a derivative of heterochain polyamines, containing highly polar N-oxide groups, leads to an increase in the number of CD4-CD8 + thymocytes, without changing their ratio with CD4 + CD8- cells [10]. In the works of D.A. Sharshembiev [2] showed that after 3-fold administration of polyoxidonium in therapeutic doses to mice in the first 14 days, the area of the thymic cortex increases with a simultaneous decrease in the area of the medulla. The authors suggest that the revealed change in the cortical-cerebral index is associated with the activation of lymphocytopoiesis in the organ. It was found that the use of polyoxidonium for 3 weeks reduces the degree of development of accidental involution of the thymus caused by removal of the spleen and contributes to the correction of the immunodeficiency state [7].

In an experiment on white outbred male rats [11] who were injected intramuscularly with cyclophosphamide, imunofan and their combinations, it was found that the course administration of imunofan leads to changes in the
morphology of the thymus and the functioning of its bio-amine-containing structures. Imunofan significantly increases the width of the cortical, diameter and area of the medulla of the thymus with a corresponding increase in the mass of the organ 7 and 14 days after the end of the course of injections. An increase in the number of luminescent granular cells of the cortico-medullary and subcapsular zones after 1 and 14 days is revealed. After 14 days, the cells of both the cortico-medullary and subcapsular zones become larger and more densely filled with granules. It has been shown that the use of Imunofan against the background of the introduction of cyclophosphamide promotes an increase in the mass of the thymus, the size of the cortex and medulla of the lobules, and accelerates the restoration of the cytoarchitectonics of the thymus. Recovery processes occur within 1 day after the combined course. After 7 days, the weight of the thymus and the size of the cortex and medulla in rats with isolated administration of cyclophosphamide and in the group with combined administration of cyclophosphamide and imunofan differ little, but there is a tendency towards normalization of the thymus structure. After the combined administration of imunofan and cyclophosphamide, the structure of the thymus and bioamino supply of cells differ significantly from those with the isolated administration of both drugs. It was found that an increase in the size of the cortical and medullary substance of the lobules with the introduction of imunofan occurs due to the activation of proliferation and differentiation of thymocytes, which can be mediated by the inclusion of the production of factors that control the growth and development of lymphocytes [14]. Imunofan reduces the degree of destruction of lymphocytes, since it has the ability to protect their DNA from damage caused by cyclophosphananum [9], thereby reducing the degree of involutive changes in the thymus, and also accelerates the processes of restoration of the thymus structure after acute involution induced by cyclophosphananum ... Imunofan stimulates the production of IL-2 by immunocompetent cells and increases the sensitivity of lymphoid cells to this lymphokine [14].

Much attention is paid to the study of the effect of stress factors on the organs of the immune system at the early stages of ontogenesis, since it is during this period that the immune system is most sensitive to the effects of most pathogens [9, 11].

A comprehensive assessment of the immunoarchitectonics of the thymus revealed some important tendencies regarding the development of stress-induced immunomodulation in the growing organism of experimental animals under the action of various types of stressors (physical and psychoemotional). According to quantitative immunohistochemical analysis, among the mechanisms of involution
of the thymus during chronic stress in a growing organism, excessive apoptosis of double positive T-lymphocytes of the cortical substance and suppression of the proliferation of cortical thymocytes are of great importance [2]. It has been shown that under chronic stress there is a decrease in the number of T-lymphocyte precursors in the red bone marrow and a decrease in the level of their chemoattractants in the thymus, which contributes to organ hypoplasia.

[15].

According to the authors, the cause of accidental involution is considered to be an increase in the migration of thymocytes from the thymus to the blood and peripheral immune organs [8]. The carried out immunohistochemical studies made it possible to conclude that under chronic stress there is no increase in the number of early thymic immigrants (Thyl.1 + cells) in the peripheral organs of the immune defense, there is a decrease in the content of this fraction in comparison with age control. Consequently, in the early stages of postnatal ontogenesis, the main mechanisms of thymic involution in chronic stress are excessive death of double positive thymocytes and inhibition of their proliferation [7].

During the experiment on animals exposed to chronic immersion-immobilization stress for 7 days, 5 hours daily, the distribution of NK cells in the compartments of the spleen and lymph nodes in different age periods of early postnatal ontogenesis. The dynamics of stress-associated changes in immune parameters related to innate immunity is shown. The study showed that experimental animals of all age groups have an accidental involution of the thymus and spleen. Microscopically, involute changes characteristic of chronic stress were revealed in the spleen, manifested in hypoplasia of the white pulp: a decrease in its volume, a decrease in the number of lymphoid nodules, an almost complete disappearance of germinal centers, narrowing of the inner and outer zones of the periarterial lymphoid sheaths (PALV), an increase in the frequency of apoptosis of lymphoid cells not only in lymphoid nodules, but also PALV, narrowing of the marginal zone. CD8 + immunoreactive cells were present in control animals of all age groups, predominantly in the SALV of the spleen. A quantitative immunohistochemical study showed the presence of immunosuppressive changes in the spleen of rats of all studied age groups, which related to the parameters of natural immunity - the number of NK cells in peripheral immune organs (NK cells are the main component of innate immunity) [4].

The authors in chronic experiments on growing rat pups aged 21-30 days studied the effect of hypodynamia and hypo-kinesia on the micromorphology of the thymus. It was established that the dynamics of structural changes in the thymus under the influence of prolonged limitation of motor activity is
characterized by the death of lymphocytes, a decrease in their relative density in the cortex of the organ lobules, and an increase in the volumetric density of the interlobular connective tissue. The revealed changes in the process of postnatal thymus development indicate a decrease in the functional capabilities of the developing organism, and the degree of these changes is directly proportional to immobilization and inversely proportional to the age of the animal [13]. Single Hassal bodies were found inside the lobules in control animals of the age under study. In experimental animals, a significant decrease in the mass of the thymus was noted in comparison with the control of the same age, which indicates a violation of the processes of growth and formation of the organ. A greater number of fibroblasts, adipocytes, collagen fibers in the capsule and interlobular trabeculae were found in comparison with the control. Among the elements of the intralobular stroma, the appearance of a large number of Gassal's bodies and accumulations of epithelioreticulocytes in the medulla should be noted. At the same time, an increase in the specific density of epithelium in the medulla was observed. Thus, in the thymus of immature rats under conditions of prolonged limitation of motor activity, a change in vascular-stromal relationships was noted due to an increase in the number of stromal elements and hemodynamic disturbances [16].

In the postnatal period of ontogenesis, the development of the lymphoid tissue of the spleen is significantly activated, the rate and extent of which is largely determined by the strength of antigenic stimulation, and these processes improve from the moment of birth to 10-12 years of age [12].

Studies show that the spleen is structurally formed by the age of 10, and two mutually opposite processes are observed in ontogenesis - an increase in the amount of one tissue while a decrease in the other. In the spleen, there was a steady growth of connective tissue with a decrease in lymphoid tissue [15]. The presence of lymphoid nodules in the organs of the immune system is a reliable morphological criterion for their functional maturity [11].

In the work of V. Kh. Khavinson (2010), a study of the organs of the immune system of rats subjected to γ-irradiation was carried out. In the irradiated animals, the internal organs were moderately anemic, the mesenteric lymph nodes were dark in color. The thymus and spleen were reduced in size. The spleen weight varied from 220 to 400 mg, the thymus mass - from 90 to 140 mg (in the control group, it was 570-870 mg for the spleen, and 400-550 mg for the thymus). On histological sections, the size of the lobules was significantly reduced. The division into cortical and medullary substance was erased, and in some lobules the boundary between the layers disappeared. Similar involutive changes are also revealed during natural aging of the thymus in persons over 60 years of age. The
number of cells in the cortical substance decreased, however, the proliferative activity of thymocytes according to the PCNA index increased in comparison with the control (23.6 ± 1.4%), which indicates post-radiation restoration of thymic tissue. In the medulla, destructive changes were less pronounced. The ratio between the parenchyma and the stroma was violated in the direction of the increase in the latter. There was an edema of the vessels of the connective tissue septa. The stroma was swollen, edematous, with fatty infiltration along the periphery of the lobules. After irradiation, the spleen tissue showed contraction of the white pulp and atrophy of the periarterial muffs. In place of the lymphoid follicles, central arteries were visible, surrounded by a narrow rim of perifollicular reticular tissue, in which single accumulations of decaying lymphocytes, plasma and reticular cells could be found. The walls of the blood vessels of the white pulp and connective tissue trabeculae were edematous and partially homogenized due to plasma impregnation. The peripheral sinuses in the spleen were overflowing with blood, and the stroma in the subcapsular zone was practically bare. The number of cells in the subcapsular zone decreased by more than 2 times, however, along the periphery of the spleen, the proliferative activity of cells according to PCNA increased to 58.3 ± 3.0% (control 35.4 ± 1.0%) [6].

When studying the spleen in the offspring of mothers with toxic liver damage caused by injections of heliotrin for 6 weeks, significant changes in the structural parameters of the formation of the spleen of the offspring in early postnatal ontogenesis were established. In experimental rat pups, the formation of T- and B-dependent zones of the white pulp of the spleen occurred generally 5-7 days later than in the control group. They retained the foci of hemocytopoiesis much longer in comparison with the control. Obviously, this is the result of the later formation of red bone marrow in the experimental group of rat pups.

Bibliography


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