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Morphofunctional Changes in the Thymus Gland under the Influence of Psychogenic Factors

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ABSTRACT

In the thymus of animals subjected to acute stress, a decrease in lymphoid tissue was found, accompanied by the death of lymphocytes in the cortex and medulla. Acute stress leads to the appearance in the thymus of a large number of degranulating mast cells and actively functioning epithelial tubules.

Psychological stress has great impacts on the immune system, particularly the leukocytes distribution. Although the impacts of acute stress on blood leukocytes distribution are well studied, however, it remains unclear how chronic stress affects leukocytes distribution in peripheral circulation. Furthermore, there is no report about the role of spleen in the blood leukocytes distribution induced by stress. Here we show that spleen contributes to the alteration of restraint stress induced blood leukocytes distribution. Our data confirmed that restraint stress induced anxiety-like behavior in mice. Furthermore, we found that restraint stress decreased the CD4/CD8 ratio and elevated the percentages of natural killer cells, monocytes and polymorphonuclear myeloid-derived suppressor cell. We demonstrated that activation of hypothalamic-pituitary-adrenal axis (HPA) and sympathetic nervous system (SNS) contributes to restraint stress induced alteration of blood leukocyte distribution. Interestingly, we found that splenectomy could reverse the change of CD4/CD8 ratio induced by restraint stress. Together, our findings suggest that activation of HPA axis and SNS was responsible for the blood leukocyte subsets changes induced by restraint stress. Spleen, at least in part, contributed to the alteration in peripheral circulation induced by restraint stress.

KEYWORDS: *Lymphocytes, thymus, stress, pain, histopathological changes, environment, morphology, external factors, experiment, Gassal cells, epithelial cords, Thymic Atrophy, ThymicHyperplasia, T-cells.*

INTRODUCTION

The experiment involved 30 animals - non-inbred white rats (males and females) of four months of age with a body weight of 150-200 g, kept under standard vivarium conditions (free access to food and water and 12-14-hour daylight hours). Two experimental groups of 10 animals each were formed: I - intact animals in standard vivarium conditions; II - rats subjected to acute cold stress, which was modeled as follows: a single exposure to a temperature of +5 ° C, exposure - 1.5 h. Daily observation of animals included registration of behavior, appearance, physiological functions. On the 7th day, the animals were removed from the experiment under ether anesthesia in compliance with the rules of euthanasia, and the autopsy material was taken for subsequent histological examination (thymus).

The thymus is covered with a thin capsule of dense unformed connective tissue with a large number of collagen fibers and is divided by trabeculae into indistinctly delimited lobules, consisting of cortical and medulla. In some animals, adipose tissue is found in the trabeculae. In some preparations, the border between the cortex and the medulla is not clearly revealed. The cortical substance of the thymus is represented by weakly oxyphilic epithelioreticular cells, macrophages and basophilic-stained, tightly adjacent T-lymphocytes; a small number of capillaries surrounded by epithelioreticular cells are found in it.

The thymus medulla looks lighter. Lymphocytes, macrophages and epithelioreticular cells are well visualized in it. At high magnification, thymic bodies formed by reticuloepithelial cells are revealed. In the connective tissue of the thymus septa, single mast cells are detected.

In the group with cold stress, by the 10th day of the experiment, the thymus tissue showed, first of all, vascular disorders (edema of the connective tissue and vascular congestion). As for the changes in the lymphoid tissue, they were expressed to varying degrees in different lobules in the same individuals.

In some experimental rats of this group, the disappearance of inversion of layers in individual lobules of the thymus was noted - with the depletion of not only the medulla, but also the cortical layer of the thymus, which was manifested by the depletion of the layers with cells of the lymphoid series and the disappearance of clear boundaries between the layers.In the medulla and cortical layers of the thymus, areas of lymphocyte death were visualized, which manifested itself light-optically as a "picture of the starry sky." In 20% of animals in the lobules, the replacement of lymphoid tissue with adipose tissue was noted.

Main part

The influence of various pathogenic factors on human health leads to morphological changes in tissues, disruption of the function of individual organs, and in particularly severe cases, the entire body as a whole. All this forces scientists to pay close attention to the organs of immunogenesis that provide the body's defense mechanisms [1-6].

The blood system plays an important role in the body's response to any stressful effect [7]. In recent decades, the influence of stress on the mechanisms of regulatory processes in humans and animals has been actively studied, its role in the adaptation process with the participation of cytokines and antioxidants has been shown on models of emotional, pain, traumatic and other stresses and also the fact that under the action of stress, all regulatory information goes from the nervous system through the pituitary-adrenal, lymphoid system and hematopoietic organs, and the general adaptation syndrome develops against the background of the restructuring of the activity of the local microenvironment, in which stromal elements and cytokines play an important role [7]. Nevertheless, today there are many unresolved issues in the pathomorphological changes in the organs of immunogenesis under stress, which determines the relevance of research in this direction.

The process of age-related involution,an evolutionarily ancient process inherent in all vertebrates, stands apart [15]. One of the characteristic features of true age involution is its irreversibility under physiological conditions. Recovery of the thymus after involution due to gonadectomy, administration of luteinizing hormone or growth hormone is shown.

An absolute decrease in thymus mass correlates with the onset of puberty. The thymus, which has undergone age-related involution, is an accumulation of adipose tissue with remains of the parenchyma containing islets of epithelial cells and thin strands of a few thymocytes with Gassal cells. However, involution is never complete,small islands of the thymus parenchyma are found even in people older than 80 years [16].

In all animals of the group (100%, $p < 0.05$ with respect to control), inversion of layers was also observed, which is typical for the 3rd phase of accidental thymic involution under stress [8].

The blood vessels in the devastated cortex had a structure typical of the vessels of the thymus medulla. It is known that the hemocapillaries of the cortical layer have a relatively thick basement membrane, to which epithelioreticulocytes, macrophages and lymphocytes often adjoin; the basement membrane of the medullary hemocapillaries, on the contrary, is thin [7].

Also, in the cortex and medulla, areas of stromal collagenization and the formation of a large number of thymic bodies were detected.

In the thymus tissue, a large number of mast cells were detected - large cells with basophilic granules. They were found mainly in the interlobular connective tissue, in the connective tissue of the septa inside the lobules in the vicinity of the blood

Mast cells are an integral part of the thymic microenvironment; their main function is to control the composition of tissue fluid, they are regulators of tissue homeostasis and the last link in the general adaptation reaction at the cellular level, in the thymus they are actively involved in the processes of differentiation and migration of thymocytes [13]. In 70% of animals, epithelial tubules lined with cubic epithelial cells were also detected in the cortical layer of the lobules.

It is known that epithelial tissue plays a leading role in the implementation of the functions of the thymus; at the same time, both in the human thymus and in the thymus of laboratory animals, epithelial tubules, thymic bodies and epithelial accumulations are permanent structures [13]. In 2009, only one term was introduced into the nomenclature, referring to the epithelial structures of the thymus, thymic body; the combination of three types of epithelial formations of the thymus (epithelial cords, epithelial tubules and thymic bodies) under one general term is conditional and inhibits the development of ideas about the structure of the thymus [12].

Most researchers explain the proliferation of epithelial structures in the thymus by the emergence of an urgent need to enhance the secretion of thymic hormones under extreme exposure [9, 10]. The cavity forms of the tubules can be constantly determined with the tension of the functional activity of the thymus, expressed in a change in the emigration and immigration of lymphocytes in the organ - not only in the embryonic, early postnatal and senile periods of genesis, but also under the influence of stress factors on the body. In accordance with modern ideas about the functions of the thymus, all these periods of life characterized by an unbalanced supply of T-precursors from the bone marrow to the thymus and emigration from the thymus to the peripheral lymphoid organs of T-lymphocytes that have passed the intrathymic stage of maturation; at the same time, not only mature T-lymphocytes migrate from the thymus to the lymphoid organs, but also immature forms, which are able to mature in these organs under the influence of thymic factors [12].

Thus, when comparing the data of histological examination of the organs of animals of the experimental and control groups, the following patterns were revealed. In rats subjected to acute stress, changes in the organs of the immune system were found, characteristic of acute stress, a decrease in lymphoid tissue - in the thymus

The study of the thymus as a central organ of the immune system under stress is of particular interest to date.

Later, many researchers have shown that accidental involution of the thymus develops not only when exposed to an infectious agent, but also when various factors affect the body [7].

Under stress conditions, incidental involution of the thymus reflects suppression of its function [11]. Generalization of the information available to date in the literature makes it possible to represent this process as a sequential change of five phases; at the same time, the processes of death and migration of T-lymphocytes in different lobules are uneven, and the absence of strict parallelism of changes in lobules is reflected in the morphological picture of one stage or another, in addition, the nature of the response of the thymus to the stressor depends on the nature of the stressor [7].

At the same time, according to other authors, lymphopenia in lymphoid organs during stress reaction develops not as a result of cell breakdown, but due to a decrease in neoplasm and increased migration of lymphocytes from these organs to the bone marrow with the formation of a “lymphoid peak”. It is known that lymphocytopenia accompanies stress practically throughout all its stages, but it is most pronounced in the stage of anxiety and in the stage of exhaustion (especially), which is characterized by almost complete atrophy of the thymus [14].

Thus, in the central and peripheral organs of immunogenesis of animals subjected to acute cold stress, we observed similar changes, which are manifestations of acute stress, the reduction of lymphoid tissue. In the thymus, the reaction of reticuloepithelial structures and mast cells was also revealed.

With acute stress exposure, the central nervous system is activated, which triggers a stress response. It consists in the fact that the peripheral nervous system is activated, and various hormones begin to be released by the endocrine glands. In the body, there is a violation of biochemical processes, which leads to undesirable changes in tissues and organs. The organs responsible for immunity are affected. In the blood, the level of hormones - glucocorticoids, a high concentration of which suppresses the body's immune system, sharply increases. In acute stress, the gender difference is sharply manifested. In female rats, after acute stress, the immune response increases significantly, resulting in faster recovery. In males, the reaction is the opposite, so healing is slower. This study also confirms human sociology, according to which socially isolated men are more difficult to tolerate stress and illness than isolated women. Scientists do not know why women are quicker to restore your immune system after stress than men. Perhaps this is due to the fact that in this way they subconsciously protect the health of their future children. Thus, men who are socially isolated are more susceptible to diseases and live less than women who are isolated. Scientific studies in laboratory mice have shown that short-term stress increases the strength and duration of the immune response. In another study, in which mice were placed for two hours in the same cage with more aggressive counterparts, it was found that such stress increased the response to the flu virus. Acute positive stress strengthens the immune system regardless of gender and accelerates the healing process of minor injuries. In the case of short-term stress effects, in contrast to the effects of chronic stress, there are no clinical manifestations of psychological and physiological dysfunctions associated with a violation of the immune system. Underestimation of the state of health, inadequate treatment and, as a result, aggravation of the picture of the disease can be dangerous here [18].

The restoration of the structure and function of the immune defense occurs gradually. At first, the cell depots begin to fill up, because due to the decrease in the stress effect, there is no need for an increased content of immune cells in the periphery. There is time for the maturation of cellular elements. Soon the periphery is filled with mature immune cells necessary for the life of a healthy body. For future acute stress, there is a reserve of mature and maturing elements in the depot and organs of the immune system. When restoring psychophysiological functions, if the stage of exhaustion has not occurred, and the sympathetic part of the nervous system dominates, with relaxation or active correction, the immune system normalizes [17, 19].

Research results

The experiment involved 30 animals - non-inbred white rats (males and females) of four months of age with a body weight of 150-200 g, kept under standard vivarium conditions (free access to food and water and 12-14-hour daylight hours). Two experimental groups of 10 animals each were formed: I - intact animals in standard vivarium conditions; II - rats subjected to acute cold stress, which was modeled as follows: a single exposure to a temperature of +5 ° C, exposure - 1.5 h. Daily observation of animals included registration of behavior, appearance, physiological functions. On the 7th day, the animals were removed from the experiment under ether anesthesia in compliance with the rules of euthanasia, and the autopsy material was taken for subsequent histological examination (thymus).

Chronic stress has a marked regulating effect on the immune system of growing animals, one manifestation of which is the change in the structural and immunocytochemical characteristics of the thymus, typical immunosuppressive conditions, namely: reduction in size of the thymus and a decrease in its cellular density, reduction of cortico-cerebral ratio, the number СБ90+ and СБ8+ thymocytes in the cortical substance of the thymus, DBA+thymocytes in the cortex and the medulla of the thymus, increased death of thymocytes and inhibition of their proliferation in the cortical substance of the thymus.

The sensitivity of the immune system of a growing organism to the action of various types of stressors (physical versus psychoemotional) depends on the initial age. According to an immunohistochemical study, physical stressors cause a sharp immunosuppression in infancy, while emotionogenic stressors significantly less change the immunoarchitectonics of the organ during this period. In the suckling period, a greater sensitivity of the thymus to the action of physical stressors remains with an increase in the strength of the immunomodulatory action of psycho-emotional stressors, and by the end of the infantile period, the immunosuppressive effect of emotsiogenic stressors is practically compared with that of physical stressors.

Conclusion

The thymus of immature experimental animals of the age of transition to independent nutrition is the most sensitive to the immunosuppressive effect of chronic stress, which, according to immunohistochemical research, causes the highest degree of accidental involution of the thymus in animals of the suckling period compared to animals of the infant and infantile periods.

The leading mechanisms of thymus involution in chronic stress in a growing organism are excessive apoptosis of double positive thymocytes of the thymus cortex and inhibition of lymphocyte proliferation in it.

Immunohistochemical methods of research significantly expand the possibilities of assessing the dynamics of thymus immunoarchitectonics under stress, among them the most informative are staining on CD8, PCNA and ED1, which allows not only to state the presence and direction of changes, but also to decipher their mechanism.

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