INTEGRATED NEURO-IMMUNO-ENDOCRINE INTERACTIONS IN HUMAN PHYSIOLOGY: MECHANISMS AND FUNCTIONAL SIGNIFICANCE

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Abstract From the perspective of modern science, the study of various aspects of the functioning of a single neuroimmunoendocrine system is one of the most pressing problems of experimental medicine and biology. A significant number of facts have been accumulated that consider the immune system together with the nervous and endocrine systems as a multi-component morphofunctional General regulatory system. The interaction of the nervous, immune and endocrine systems ensures the normal functioning of the body, and, undoubtedly, these three systems maintain the constancy of the body's environment, serving as a "triangle of homeostasis". The study of morphofunctional bases of General regulatory reactions, mechanisms of cell signaling in the formation of connections between various structures of the neuroimmunoendocrine system in order to preserve homeostasis is relevant.

Keywords: neuroimmunoendocrine, immunophysiology, immunogenesis, immunocompetent cells, neuropeptides.

The subject of neuroimmunoendocrinology research is the study of extraimmune (nervous, hormonal, and other humoral) mechanisms for regulating the functions of the immune system in the entire body and the role of immune mechanisms in the functioning of the neuroendocrine system [1].

Modern trends in the study of General neuroendocrine, neurochemical and immunological aspects of changes in the functioning of the body allowed us to

formulate the concept of interdependence of physiological and pathological processes in the Central nervous, immune and endocrine systems [2]. Ideas about the mechanisms of development of most pathological conditions that arise as a result of the influence of various factors are formed taking into account the huge contribution to this biological process of neuroimmunoendocrine structural and functional connections formed in those organs in which the largest number of cells of this system is concentrated [9]. The structure of the neuroimmunoendocrine triad, despite the strict interdependence of all its components, has an element of hierarchy. The cornerstone of neuroimmunoendocrine interactions is the Central nervous system (CNS). Therefore, it seems promising to study the mechanisms of Central regulation of life support systems, including the immune system. This will serve as one of the main conditions for successful therapy of various pathologies, in the development of which immune disorders play a role [6].

Data confirming the influence of the brain on the functions of the immune system were obtained as early as 1891, when Savchenko I. G. first showed that cutting the spinal cord makes pigeons susceptible to anthrax; a similar effect occurs when removing the hemispheres of the brain. For the first time, the antigenic properties of the brain were demonstrated by I. I. Mechnikov in 1901, and later the cytotoxicity of the blood serum of an animal immunized with an extract from brain tissue was proved. The world-recognized founder of systematic research in the field of immunophysiology is considered to be S. I. Metalnikov, who in 1925 formulated the idea and raised the question of the possibility of the existence of regulating effects of the nervous system on the protective functions of the body and conducted the first experiments in this direction. The next stage in the development of immunophysiology was the study of innervation of lymphoid organs in the works of Bulloch K. (1985) and Tollefson L. (1989). An important step in the study of this area was the research of Bulloch K. (1985), related to the study of the significance of various neurotransmitter systems in the regulation of immunogenesis. In the 60s

of the xx century, the study of hisa and Krapp was considered promising in the development of this direction, in which the authors, using the method of immunofluorescence, concluded that in schizophrenia there is an atypical immunoglobulin that reacts with elements of brain tissue [15].

According to most researchers, the immune system is a disseminated mobile "brain". The immune system, along with the Central nervous system, is able to recognize, remember, and extract information from memory. In this case, the carriers of neurological memory functions are neurons of the analyzer and limbic systems of the brain, and the carriers of the immunological memory function are certain subpopulations of Ti B-lymphocytes, called memory lymphocytes [9,7].

Numerous studies, both experimental and clinical, have revealed the factors by which intersystem connections between the nervous, immune and endocrine systems are realized in various conditions [7].

There are several ways to transmit control signals from the brain to the immune system: through neurotransmitter systems; hormonal pathways, when the endocrine glands, obeying CNS signals, change the amount and ratio of released hormones and thereby affect the function of the immune system; as well as through the involvement of neuropeptide molecules that regulate the intensity of cells and organs of the immune system [3].

It was found that various neuroendocrine mediators can selectively modulate the immune system, affecting the proliferation of immunocompetent cells and their production of cytokines [12]. At the same time, the mechanisms of feedback of the immune and neuroendocrine systems, implemented through mediators of the immune system, primarily cytokines, were also identified [13]. Ideas about the mechanisms of three-system interaction have significantly expanded in recent decades due to the discovery of effector cells that produce substances that carry it out, and target cells identified in both the immune and neuroendocrine systems [8-10]. Close relationships between the three regulatory systems occur in each visceral

organ via peptide / aminergic neurons [14], immunocompetent cells [16] and apudocytes [17].

If we analyze numerous studies of scientific schools, the scheme of neuroimmunoendocrine interaction is as follows: neuroactive substances in one of the above ways penetrate the innervated tissues and affect the processes of immunogenesis, while changing the chemical environment of cells that protect. Changes in the chemical composition of neurotransmitters are perceived by receptors on the membranes of lymphocytes, and cells begin to respond to shifts in the quantitative ratio of hormones and neurotransmitters in their environment. Meeting with a foreign protein, the cell responds with a complex of reactions, while other cells are involved in the process and various biologically active factors are synthesized. Conversely, the immune system receives signals that accelerate or slow down axonal transport, depending on the chemical nature of the influencing factor. Cells of the lymphoid tissue produce humoral factors that are also synthesized by cells of the nervous and endocrine system (norepinephrine, acetylcholine, serotonin, substance P, somatotropin, corticotropin, vasopressin, oxytocin, etc.), and in the nervous tissue and endocrine system, interleukins, interferons, and a number of other mediators of immunomodulation are secreted [2, 8, 10, 16].

In immunoregulation, the most significant corrective influence, according to most researchers, is provided by brain structures that modulate the intensity of the immune response, namely, the anterior and posterior hypothalamic fields, the hippocampus, the suture nuclei, the reticular formation of the midbrain, and the amygdala complex [14]. Participation in the regulation of immunogenesis of the cerebral cortex, septum, basal nuclei, and limbic system proves the relationship between cognitive functions and immunomodulation [10].

The role of Central neurotransmitter (serotonergic, GAMA ergic, and dopaminergic) systems in regulating the functioning of the immune system has been proven in recent decades. It was found that the membrane of immunocompetent cells

has specific receptors for glutamate, dopamine, serotonin, gamma-aminobutyric acid (GAMA), etc.[2]. When studying the biochemical mechanisms of neurotransmitter action on the metabolism and functional activity of cells of the immune system, it is shown that signal transmission occurs through the system of cyclic nucleotides (cGMP, camp), calcium flows, membrane ATP-azes, through the sphingomyelin pathway [3].

It was found that activation of the GABAergic and dopaminergic systems contributes to an increase in immunological reactivity, while stimulation of the serotonergic system causes a decrease in immunogenesis [13]. In this case, the implementation of the immunomodulatory action of neurotransmitter systems is possible only with the integrity of the hypothalamic-pituitary complex [3]. Data indicating the presence of NMDA receptors in cells of lymphocytic morphology confirm the existence of glutamate regulation of immunocompetent cells [4].

In recent years, the important role of peptidergic regulation mechanisms in the processes of proliferation and differentiation of nerve and immunocompetent cells through neuropeptides, thymus peptides, myelopeptides (MP) and their synthetic analogues has been proved [13, 15].

Researchers are interested in studying the role of neuropeptides in regulating the immune response and directly neuroimmune interactions. It was found that neuropeptides contain up to 50 amino acid residues and interact with specific membrane receptors, while the size of the active center, as a rule, does not exceed 4-5 amino acid residues, while the rest of the neuropeptides perform additional functions, for example, determine the features of interaction with proteolytic enzymes. Numerous experimental studies indicate the secretion of neuropeptides into the blood by cells of the pituitary, adrenal, thyroid, APUD-system, as well as from the peripheral nervous system to innervated tissues (including lymphoid). The discovery of neuropeptide receptors, along with the ability of immunocytes to produce neuropeptides, highlights their involvement in intersystem cooperative

responses. Neuropeptides regulate almost all functions of the Central nervous system (pain sensitivity, sleep—Wake state, sexual behavior, information fixation processes, etc.).

In addition, neuropeptides control vegetative responses of the body, regulating body temperature, respiration, blood pressure, muscle tone, etc.Neuropeptides control stress-induced changes in the immune system, and mediate integrative interaction of the immune and nervous systems, changing, in particular, the levels of subpopulations of circulating lymphocytes and eosinophils and cytokines, respectively [10].

Studies on the role of neuropeptides and neurotransmitters in skin repair processes in infectious-inflammatory, autoimmune, and allergic diseases confirm the important role of neuropeptides and neurotransmitters in the regulation of immune system functions [17]. The complex pathogenesis of diseases is not limited only to inflammation developed as a result of aggressive exogenous factors, but also includes mechanisms of neurogenic inflammation involving neuropeptides. The discovery of the mutual connection between the immunological and neurogenic links of the inflammatory response is considered as one of the most significant achievements in clinical pulmonology and Allergology. Allergic inflammation in the skin has been shown to induce neuronal dysfunction, thus modulating inflammation-related changes in damaged tissues. There is also evidence of neuronal regulation of inflammatory processes in the skin. In addition, there is evidence that structural skin cells and immunocytes Express neuronal receptors and secrete neurotransmitters. Neuropeptide receptors, cytokine receptors, or chemokine receptors along with histamine receptors have been shown to play an important role in the pathophysiology of allergic skin diseases. Neuropeptides secreted by skin sensory neurons have a high affinity for epidermal cells, changing the functions of keratinocytes, Langerhans cells, mast cells, skin capillary endothelial cells and skin immunocytes, determining the development of skin diseases. During an allergic

reaction, skin cells not only serve as a source of neurotransmitters, but also serve as a target for the action of neuropeptides or neurotrophils. This can become the basis for further research on the development of pathways for neuropeptide and neurotransmitter pharmacocorrection [18].

It was also found that signals from the Central nervous system reach the organs of the immune system with the participation of the parasympathetic and sympathetic divisions of the autonomic nervous system [10]. The main vegetative center that regulates the functions of the immune system is the hypothalamic region of the brain [1]. The principal possibility of influencing the intensity of immunological processes by irritating hypothalamic structures was first shown in the work of Groote J. and Harris G., who, irritating mammillary bodies and the gray hillock of the hypothalamus (GT), observed inhibition of immune responses [11]. There is still no single point of view regarding the exact localization of the immunoregulatory center in the hypothalamus. Thus, according to some authors, the lateral part, and according to others — the medial part of the preoptic region of the GT serves as an integrative center that regulates the functions of the immune system. However, it is likely that there is a certain specialization of the hypothalamic zones in relation to immunoregulatory functions. Thus, the cytotoxicity of natural spleen killers is suppressed by the medial preoptic part of the GT through sympathetic innervation, and electrical stimulation of the lateral GT leads to significant activation of NK cells [12]. At the same time, when comparing experimental groups of rats with damage to the ventromedial region of GT and falsely operated ones, it was shown that this region may be receiving immunogenic signals, but it does not serve as a center of neuroimmunomodulation [9]. In favor of lateral GT nuclei, data obtained by implanting electrodes in these structures, which under the influence of electrical impulses stimulate the response to the introduction of T-dependent antigens: sheep red blood cells (EB) and bovine serum albumin (BSA). According to literature data, this region of the brain supports the structure of lymphoid organs and functional

integration in the immune system [7]. In the study of the effect of podbut-gorya irrigation on antibody titers, it was possible to state the stimulating (or depressing at high current strength) effect of GT irritation on antibody formation [15]. The results of experiments with Paraventricularis N. and Supraopticus N. show that the neuro-secretory parts of the hypothalamus are the center of the neuro-immunoendocrine system [12].

In the works of I. G. Akmaev and co-authors on neuroimmunoendocrinology of the hypothalamus, it was found that in the conditions of acute and chronic immune stress induced by the introduction of E. coli lipopolysaccharide (LPS), changes were observed in all links of the neuroimmunoendocrine network. In acute immune stress (single administration of LPS at a dose of 250 mcg/100 g), an increase in corticoliberin secretion was noted, which eventually led to an increase in the secretion of adrenocorticotropic hormone (ACTH) in the pituitary gland and, accordingly, corticosteroids (CS) in the adrenal glands. Chronic administration of LPS in doses from 25 to 250 mcg/100 g for 13 days, on the contrary, inhibited the secretion of releasing hormone in GT, while the secretion of ACTH and CS remained at the same high level. At the same time, the secretion of immune mediators, especially IL-1, was increased. In the course of research, it was concluded that cytokines, in particular IL-1P, secreted by cells of the anterior pituitary (GF), act as a stimulator of ACTH in chronic hyperimmunization of LPS. Cytokine secretion in cells of the anterior lobe of the GF and in neurons of the paraventricular nucleus is prostaglandin-dependent and increases with the action of LPS [13].

The neuroendocrine system is the highest regulator of immune-inflammatory reactions. In particular, prolactin and growth factor stimulate the growth, differentiation and functioning of immunocytes. Neuropeptides of the hypothalamic-pituitary-adrenal system (HHNS) (ACTH, corticotropin, melanocyte-stimulating hormone, b-endorphin) affect lymphocytes through gluco-corticoids and directly, as well as induce nerve impulses directed at the lymphoid organs. In this series of

immune system regulators, the ACTH-adrenal axis manifests itself as an antagonist of growth factors and prolactin, which in turn have an immunostimulating effect [54].

Hypothalamic signals are transmitted through neurotransmitters that are perceived by the receptors of lymphoid cells, and through a system of secondary transmitters-cyclic nucleotides change the metabolism and functional activity of lymphocytes. Activation of the cGMP system is associated with the stimulation of the functions of lymphoid cells, and activation of the camp system is associated with the suppression of their functions. There is a feedback link between lymphoid cells and GT, as evidenced by the message that the inclusion of norepinephrine and epinephrine in the immune process can be induced by macrophage activation products (for example, IL — 1) on the hypothalamic region of the brain [8].

According to some researchers, the ability of the cellular elements of the hypothalamus to neurosecretion and the presence, on the one hand, when parts of the nervous and immune systems, on the other, with the peripheral endocrine glands due to hypothalamic-pituitary and paralipomena relationships determines the role of a "conductor" of the functioning of the whole organism [2, 12].

Modulation of immune responses through the sympathetic nervous system can be carried out as a result of the release of adrenaline into the blood from the adrenal medulla, the release of norepinephrine from synapses, and directly the synthesis of catecholamines in the cells of the immune system [6]. Catecholamines that secrete nerve endings can affect the proliferation and differentiation of immunocompetent cells through specific receptors in cell membranes. There is also evidence that cells of lymphoid organs participate in maintaining homeostasis at the organ level by producing biogenic amines, which determines the possibility of their influence on other immunocompetent cells, in particular those with adrenoreceptors expressed on the membrane. Thus, after antigen stimulation, the content of catecholamines increases in lymphocytes through signaling pathways initiated by protein kinase C,

which plays a key role in the activation of T-and B-lymphocytes, NK cells, and phagocytes [7]. According to other data, catecholamines inhibit T-cell proliferation, speeding up the differentiation of T-suppressors, which may also lead to inhibition of antibody formation by plasmocytes [15].

Both the stroma and the parenchyma of the lymphoid organs contain nerve endings from the parasympathetic division of the autonomic nervous system. According to the results of many studies, inhibition of acetylcholinesterase in the nervous system suppresses the immune response, so acetylcholine plays the role of an inhibitor of the immune system. In vitro, it inhibits splenocyte proliferation caused by immunization, but only before or immediately after exposure, when T-lymphocytes are activated by muscarinic cholinergic receptors. In contrast, the humoral response to EB in rats inhibits the production of acetylcholine in the CNS. According to other researchers, acetylcholine activates immunostimulation, in particular, it was shown that during the humoral immune response to EB administration (3-6 days after immunization), the activity of acetylcholinesterase in the GT and hippocampus significantly decreased. Acetylcholine has been shown to indirectly stimulate lymphocyte proliferation due to increased production of IL-1 and possibly interferon. As is known, these humoral factors affect the proliferation and differentiation of b-link cells of the immune system, accelerating the formation of Mature B-lymphocytes from pre-B elements and thereby stimulating the humoral immune response [13]. Modern data indicate that almost all populations of cells involved in immune responses are equipped with hormone receptors in addition to specific receptors for factors that implement the immune response, to neurotransmitters, which determines the possibility of modulating the effect of these agents on the functions of immunocompetent cells [12]. The dependence of lymphocyte proliferation in primary and secondary organs of the immune system on the production of hormones such as prolactin and growth hormone is shown. These hormones allow the immune cells to respond to antigenic stimulation and cytokines.

Cytokines of immune cells induce inflammatory responses, alter the neurotransmitter activity of brain neurons and the secretory activity of the pituitary gland. Subsequently, as a rule, activation of the hypothalamic-pituitary-adrenal system by cytokines leads to immunosuppression [9].

According to recent studies, it has been established that the pituitary and epiphysis control the activity of the thymus with the help of special peptide bioregulators, called "cytomedines". The presence of receptors along with the ability of immunocompetent cells themselves to produce cytomedins creates the probability of their participation in intercellular cooperative processes [3]. Drawing an analogy with the data on the influence of neurotransmitters, we can assume that cytokines affect immune cells through specific receptors. Thus, ACTH affects the function of macrophages, T-and B-lymphocytes, increases the growth and differentiation of B-cells in contrast to the suppressing effect on antibody formation. Currently, the influence of adenohypophysial thyrotropic hormone (TSH) on the development of humoral immunity, characterized by increased antibody production, has been studied. To realize the effect of TSH, the presence of T-lymphocytes is necessary [19]. It is also proved that in the development of T-cell immunodeficiency, somatotropic hormone (STH) stimulates the proliferation and differentiation Of t-cell effectors. Lactotropic hormone also has a regulating effect on immunogenesis: in an experiment, the introduction of this hormone to laboratory animals caused a dose-dependent change in the synthesis of anti — erythrocyte antibodies: in small doses — a stimulating effect, with an increase in the dose-no effect [1]. There are also known immuno-tropic functions of chorionic gonadotropin, manifested by the induction of t-suppressors and the suppression of natural killers and cytotoxic T-cells [2]. The neurohypophyseal hormones oxytocin and vasopressin can replace the function of IL-2, which induces the proliferation and growth of T-lymphocytes, as well as protects cells from apoptosis and prevents the development of

immunological tolerance. A neuroendocrine peptide hormone of the thymus — neurophysin, whose biological activity is similar to oxytocin [9], was detected.

In recent decades, studies have noted a significant immunostimulating effect of melatonin on immune processes, which is manifested in the activation of antibody formation. The mechanism of action of melatonin is unknown, but it is assumed that melatonin acts through opioid molecules, lymphokines or other endocrine changes. It is possible that there is a direct effect of melatonin on the lymphoid tissue, since melatonin-binding receptors are found in the homogenates of the thymus and spleen membranes. Changes in the density of melatonin receptors during the day and their decrease with age were found [10]. Thyroid hormones affect various immunocompetent cells, tissues, and organs of the immune system [15]. Changes in the functional activity of immunocompetent cells correlate with hormonal dysfunctions. Almost all populations of cells that participate in immune responses are equipped with hormone receptors in addition to specific receptors for neuro - and immunomediators, which determines the possibility of modulating the effect of these agents on the functions of immunocompetent cells [5].

Thyroid hormones enhance humoral immune responses, stimulate the phagocytic activity of white blood cells, increase the ability of peripheral blood monocytes to Mature and differentiate, and regulate the function of natural killers [9]. Triiodothyronine (T3) regulates IgM and IgA production, while thyroxine (T4) acts as an inhibitor of IgG synthesis, maintaining optimal blood levels of T-active lymphocytes. T3 and T4, along with their effects on cellular and humoral immunity, also affect Erythro - and leukopoiesis [18]. The effect of parathyroid hormone (parathyroid hormone) on the immune system is manifested by a decrease in the proliferative activity of thymocytes [19, 5].

It is proved that the pancreatic hormone-insulin has pronounced stimulating properties in disorders of the immune response. There is no complete clarity about the functioning of the receptor apparatus that provides the effect of the hormone on

immunological functions. Experimental data confirmed that resting lymphocytes are devoid of insulin receptors. Antigen stimulation leads to the appearance of these receptors, which reflects the process of cell differentiation and indicates that it has acquired competence to respond to stimuli specific to these receptors [19, 2].

Conclusion. Thus, in modern literature formed a clear view that the nervous and endocrine systems modulate the immune system via neurotransmitters, neuropeptides and hormones, and the immune system interacts with the neuroendocrine system through cytokines and other immunotransfer and immunopeptides [4, 9]. And from the point of view of the theory of functional systems, immune mechanisms, acting as components of self-regulating functional systems, participate in the construction of various adaptive productive activities of the body [7]. Based on the presented literature review, we conclude that further study of the principles of integration of regulatory systems (especially in the conditions of pathology, when all the links that form homeostasis are included in the implementation of the pathophysiological pathway) and the development of methods for pharmacological correction of neuroimmunoendocrine disorders is relevant.

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