SCIENTIFIC REVIEWS AND LECTURES

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EFFECT OF PHYSICAL STRESSORS ON NEUROENDOCRINE RESPONSE IN CRITICALLY ILL PATIENTS

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A critical condition is a complex of changes that require replacement of the functions of vital organs and systems to prevent death. The set of reactions can be considered as a gradual development of physiological and pathological reactivity. The most important role in the formation of reactivity in critical conditions is played by the neuroendocrine and neuroimmune systems. The concept of the neuroendocrine system includes connections between the endocrine and central nervous systems and their relationship in the control of homeostasis. Stimulation of the immune system to a complex neuroimmunoendocrine interaction in order to avoid development of a critical condition. Cytokines and afferent pathways of the vagus nerve activate the hypothalamic-pituitary-adrenal system, as a result of which the increased secretion of glucocorticoids suppresses the activity of the immune system. The main action of thyroid hormones is manifested at the genomic level by stimulating the synthesis of many structural proteins of the body and suppressing the expression of neuronal NOS. The sympathetic link of the autonomic nervous system leads to a decrease in the release of pro-inflammatory cytokines, while the synthesis of anti-inflammatory cytokines does not change. In turn, glucocorticoids have a powerful anti-inflammatory effect by reducing the transcription of cytokines by suppressing the nuclear factor "kappa-bi" - a universal transcription factor that controls the expression of genes for the immune response, apoptosis and the cell cycle. At the same time, in critical conditions, a high level of cortisol is observed against the background of a suppressed level of ACTH. This fact is explained by glucocorticoid resistance.

The relationship between the immune system and the central nervous system when exposed to stressors leads to stereotyped responses that include autonomic, endocrine and behavioral components. But despite the extremely important role of neuroendocrine factors in the implementation of critical conditions, their significance, as well as indications and measures of influence on them, have not yet been studied in detail. Further study and the concept of endocrinopathies of critical conditions in the future will be the basis for assessing the endocrine status in order to resolve the issue of the need for substitution therapy.

Keywords: critical condition, endocrinopathy, reactivity thyroid hormones, TSH, cortisole, ACTH.

Introduction. A critical condition is a complex of pathophysiological changes in the body that require replacement of the functions of vital organs and systems to prevent imminent death. Severe physical stressors that cause a critical condition include multiple trauma, cerebral strokes, myocardial infarction, acute respiratory failure, sepsis, and various types of shock [15].

The set of complex adaptive reactions of the human body, aimed at eliminating or maximum limiting the action of various factors of the external or internal environment of the body, is presented in the form of a homeostatic algorithm, which can be considered as a step-by-step development of physiological and pathological reactivity [2]. Physiological reactivity of the organism determines its subtle differentiated response to the action of environmental factors, that is, it determines the quantitative and qualitative features of the response [2]. In this case, pathological reactivity is understood as a special form of reactivity, characterized by a relatively stable, perverted form of the body's response to the corresponding stimulus. This is reflected in new responses that do not take place under conditions of physiological reactivity, in their unusual intensity and duration [5]. Pathological reactivity can be a rescue operation or a destructive mechanism, or it can be both for the body.

In critical conditions, the most important role in the formation of the development of the physiological, and subsequently pathological reactivity of the organism, is played by the neuroendocrine and neuroimmune systems.

The concept of the neuroendocrine system includes multiple connections between the endocrine and central nervous systems (CNS), their relationship in the control of homeostasis, as well as in the formation of responses to environmental stressors [5].

At the same time, stimulation of the immune system by means of foreign pathogens leads to a complex neuroimmunoendocrine interaction in order to avoid development of a critical state. It is formed through the integration of the inflow of information from the vagus nerve, peripheral cytokine interactions with receptors in the region of organs surrounding the cerebral ventricles, cerebral vessels, and local formation of cytokines within the central nervous system. This leads to a complex neuroimmunoendocrine response during the development of a critical state [12].

The leading systems of the brain are involved in the control of homeostasis. *The hypothalamus* is the key integrative center for homeostatic regulation of neuroimmunoendocrine response. The hypothalamus is able to analyze information received from the cortex, hippocampus, thalamus, basal ganglia, reticular formation, nuclei of the medulla oblongata and spinal cord, assess the composition of cerebrospinal fluid, blood and form coordinated responses by changing the efferent innervation of the key regulatory points, which include the adenohypophysis and the neurohypophysis, brain, premotor and motor neurons of the brain stem and spinal cord, as well as autonomous preganglionic neurons [12].

The hypothalamus is a small area of the brain that is part of a neural continuum that extends from the midbrain to the basal regions of the telencephalon and is closely related to the phylogenetically ancient olfactory system [11].

The interaction of the hypothalamus with a huge number of different parts of the nervous system through afferent and efferent connections is necessary in order to coordinate all autonomic processes in the body [3, 19]. In turn, the autonomic nervous system (ANS), acting in conjunction with the endocrine system and

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various nuclei of the brain stem, regulate vital functions necessary to maintain the constancy of the internal environment of the body within narrow boundaries [3]. *The thymus, the central organ of lymphocytopoiesis and immunogenesis,* is also under the influence of the ANS, with the exception of the spleen, adrenal glands, smooth muscles of the vessels of the skin, sweat glands. They are influenced only by the sympathetic nervous system, which determines their role in the immediate stress response [3].

Limbic system. The main biological purpose of the limbic system is the formation of behavior that increases the chances of survival of an individual [3].

One of the main structures of the limbic system are the structures of the brain - the hippocampus and the amygdala. The amygdala provides important behavioral functions such as anxiety and fear. The hippocampus plays an important role in the formation of learning and memory and allows you to compare present stress with past experience, providing the most adequate response to stress. The influence of the hippocampus and amigdala on the hypothalamus and ANS is carried out through the fornix, which is the main efferent bundle of the hippocampus. The presence of a high density of glucocorticoid receptors in the hippocampus enables it to suppress the synthesis of corticotropin-releasing hormone. At the same time, one of the biological purposes of the amigdala is to activate the hypothalamic-pituitary system [5].

Catecholaminergic neurons. One of the important systems of the brain stem involved in the regulation of mind control includes catecholaminergic neurons: dopaminergic, noradrenergic, and adrenergic systems [9, 17].

Neurons containing norepinephrine are concentrated in the brain stem. Their main location is the blue spot, which also includes the nucleus of the solitary tract, the dorsal motor nucleus of the vagus nerve. Axons of blue spot cells are directed towards the cerebral cortex, hippocampus, amigdala, thalamus, hypothalamus [9].

Some of the neurons of the dopaminergic system are localized in the hypothalamic nuclei, the axons of which end in the median eminence [37]. Axons of the other part of neurons are located in the periventricular space in the region of the third and fourth ventricles and are projected onto the brain stem and diencephalon [9, 21].

The efferent pathways of adrenergic neurons are located in the medulla oblongata and go to the dorsal nucleus of the vagus nerve, the nucleus of the solitary pathway, the blue pathway, the periventricular gray matter of the pons and midbrain, the hypothalamus and paraventricular nuclei [29].

Thus, the entire homeostatic system depends on the close interaction of the limbic system, which recognizes and analyzes the danger, with the hypothalamic, noradrenergic systems, which directly modulate metabolic, immune and hemodynamic responses.

"Windows" of the blood-brain barrier. Organs surrounding the ventricles of the brain serve as an important link between peripheral metabolic signals and groups of brain cells that regulate coordinated endocrine, autonomic and behavioral responses. These are specialized structures located along the midline of the brain along the third and fourth ventricles [12, 27, 35]. They include the vascular organ of the terminal plate, the subfornical organ, the median eminence, the neurohypophysis, the subcommissural organ, and the most posterior field. These brain structures are devoid of the blood-brain barrier and are "windows for the blood circulation system", allowing molecules such as proteins, peptide hormones, cytokines, lipopolysaccharides to penetrate relatively freely into the brain tissue. Thus, neurons and glial cells (microglia and astrocytes) located in the organ surrounding the brain ventricles have access to macromolecules. Some of the organs surrounding the cerebral ventricles have neuronal contacts with groups of hypothalamic nuclei that regulate homeostasis [12].

The relationship between immunoreactivity and organs surrounding the ventricles of the brain is performed due to the expression of components of the innate and adaptive immune system on its surface, such as toll-like receptors, CD14 and cytokine receptors, including receptors for interleukin (IL) 1β, IL6 and tumor necrosis factor (TNF) α [22, 25, 32].

The hypothalamic-pituitary system is a humoral component of the complex nervous and endocrine system that reacts to the effects of internal and external stressors. The activation of the central sympathetic tract begins in the amigdala, which are zones of anxiety and stress, as well as in the numerous nuclei of the hypothalamus and reticular formation. This path, passing the midbrain, the bottom of the IV ventricle descends into the lateral horns of the spinal cord - into the first neurons of the sympathetic nervous system [3]. Increased sympathetic activity leads to a state of physical tension and readiness for stress. The influence of physical stressors begins with the activation of the adrenal medulla, secreting norepinephrine and adrenaline, which have a sympathetic effect on the peripheral vascular bed [3].

The secretion of adrenocorticotropic hormone (ACTH) by the pituitary gland is under the control of corticotropin-releasing hormone and, to a lesser extent, of antidiuretic hormone. ACTH stimulates the secretion of cortisol and other adrenal steroids, including aldosterone. Cortisol has several important physiological effects on metabolism, cardiovascular function, and the immune system [16]. The metabolic effects of cortisol include increase of glucose concentration in blood by activating the key elements of gluconeogenesis in the liver and inhibiting glucose uptake by peripheral tissues. In vascular smooth muscle, cortisol increases sensitivity to vasopressor agents such as catecholamines and angiotensin II. These effects are partially mediated by increased transcription and expression of receptors for these hormones [12].

Cytokines and afferent pathways of the vagus nerve activate the hypothalamic-pituitary-adrenal system, as a result of which the increased secretion of glucocorticoids suppresses the activity of the immune system.

Hypothalamic-pituitary-thyroid system. The biological effect of thyroid hormones (TG) depends on the coordinated function and interaction of all components of *the hypothalamus-pituitary-thyroid gland-target tissue system* [1].

Thyroliberin secreted by neurons of the hypothalamus through the portal system of the pituitary gland, promotes the synthesis and release of thyroid-stimulating hormone (TSH) into the bloodstream. The secretion of both TSH and thyroliberin is regulated by a negative feedback mechanism from thyroxine (T4) and triiodothyronine (T3). TSH secretion is also corrected by other hormones, including glucocorticoids, growth hormones, and is suppressed by cytokines in the pituitary gland and hypothalamus [3].

The effects of thyroid hormones on the target tissue are a consequence of the activation of non-genomic regions - membranes, cytoplasm and mitochondria, but the main action of TG is manifested at the genomic level. TGs control the formation of heat, the rate of oxygen absorption, participate in maintaining the normal function of the respiratory center, have inotropic and chronotropic effects on the heart, increase the formation of erythropoietin, stimulate the motility of the gastrointestinal tract, and stimulate

the synthesis of many structural proteins in the body [1]. Thyroid hormones suppress the expression and inhibition of mitochondrial translocation of neuronal NOS (nNOS) [8].

The body's reactivity to physical stressors. The study of the mechanisms underlying the effect of physical stressors on the neuroimmunoendocrine response has led to the discovery of a cholinergic anti-inflammatory pathway involving the vagus nerve [44].

Chemoreceptors of the terminal part of the vagus nerve are sensitive to changes in pressure in internal organs and local changes in the chemical composition of the environment, namely, fluctuations in the concentration of IL-1, prostaglandins, TNF-α. In response to an increased level of inflammatory mediators in the organs innervated by the vagus nerve, the so-called "inflammatory reflex" is triggered [5]. This reflex is based on the transmission of information to the central nervous system, namely to the nucleus of the solitary pathway and then to the dorsal motor nucleus. All these nuclei receive information about the state of the immune system also through the chemoreceptor trigger zone of the most posterior field of the fourth ventricle [10, 42].

The efferent activity of the vagus nerve is manifested by the release of acetylcholine in close proximity to macrophages in the reticuloendothelial system, which leads to inhibition of the release of cytokines [39]. In turn, the sympathetic link of the autonomic nervous system innervates the spleen and activates T-lymphocytes, which leads to a decrease in the release of pro-inflammatory cytokines TNF-α and IL-1 by macrophages, while the synthesis of anti-inflammatory cytokines such as IL-10 does not change. Since the vagus nerve innervates the thymus and other lymphoid organs, in case of systemic inflammation, ChAT + T-lymphocytes and macrophages migrate from the thymus to the spleen, where they interact with sympathetic nerve endings, stimulating the release of norepinephrine [10]. Norepinephrine binds to β2-adrenergic receptors (β2AR) of CD4 + T-cells (T-helpers). CD4 + triggers the release of acetylcholine, which inhibits the secretion of inflammatory cytokines by macrophages through α7nAChR signaling [49].

Activation of the hypothalamic-pituitary-adrenal system by the cholinergic anti-inflammatory pathway. The afferent fibers of the vagus nerve terminate in the dorsal motor nucleus. Further, through the giant cell reticular nuclei, information about the imbalance between pro- and anti-inflammatory cytokines spreads to the blue spot of the pons, suture nuclei, amygdala, paraventricular nuclei of the hypothalamus, hippocampus and prefrontal cortex. The consequence of the activation of the hypothalamic-pituitary-adrenal axis is an increase in the concentration of corticosteroids in the blood plasma [10, 33]. In turn, glucocorticoids have a powerful anti-inflammatory effect by reducing the transcription of multiple cytokines such as tumor necrosis factor (TNF), IL-1 and IL-6. This effect is achieved by suppressing the transcriptional activity of the nuclear factor "kappa-bi". The nuclear factor "kappa-bi" is a universal transcription factor that controls the expression of genes for the immune response, apoptosis, and the cell cycle [14].

Glucocorticoids also cause a decrease in the number and change in the function of various immune cells such as T and B lymphocytes, monocytes, neutrophils and eosinophils at sites of inflammation. Another effect is to enhance the inhibition of macrophage migration, which makes a significant contribution to the regulation of the immune response to physical stressors [5]. Glucocorticoids also reduce the activity of inducible nitric oxide synthase, which has neurocytotoxicity [7, 30].

At the same time, corticotropin-releasing hormone inhibits endotoxin-stimulated production of IL-1 and IL-6 by monocytes, and ACTH suppresses the production of interferon beta-1b by human lymphocytes [46]. The fact that markers of inflammation can activate the hypothalamic-pituitary-adrenal system suggests a negative feedback loop to regulate the intensity of inflammation. But at the same time, this feedback-type reaction can have pathophysiological consequences, since chronic activation of the hypothalamic-pituitary-adrenal system by proinflammatory cytokines can lead to immunosuppression. In this case, this is a clear manifestation of the impact of pathological reactivity on the body with negative consequences [12, 36, 43].

At the same time, in critical conditions, a high level of cortisol is observed against the background of a suppressed level of ACTH. This fact is explained by the stimulating effect of cytokines on the adrenal glands. Hyperproduction of cortisol by the adrenal glands, in turn, suppresses by negative feedback the synthesis and secretion of ACTH. However, currently there is no direct evidence of the reasons for detecting high cortisol levels against the background of a decrease in ACTH levels. In addition, in some cases, there is glucocorticoid resistance, which is defined as a decrease or lack of sensitivity to the hormone, the absence or reduced effect of the hormone, despite its normal or increased level in blood [1, 28].

Activation of the hypothalamic-pituitary-thyroid system under the influence of physical stressors. Physical stressors are a determinant of TSH secretion, regardless of thyroid hormone levels [38]. Thus in the syndrome of euthyroid pathology, the low content of T3 and T4 does not cause a compensatory increase of TSH secretion. Inhibition of TSH secretion in the pituitary gland is caused by the influence of peripheral and local cytokines on the hypothalamus and, as a consequence, a decrease in the activity of the thyroid gland [24, 47].

Under stress conditions, the inhibitory effect of glucocorticoids on the secretory activity of TSH in the pituitary gland is also manifested. This influence is carried out through the expression of glucocorticoid receptors on the surface of pituitary thyrotropin-secreting neurons [20, 24].

Factors contributing to the development of pathological reactivity. The relationship between the immune system and the central nervous system when exposed to physical stressors, with the aim of returning homeostasis to its previous state, leads to stereotypical responses that include autonomic, endocrine and behavioral components. Long-term effects of cytokines on the central nervous system, activation of inducible nitric oxide synthase, hypoxia of brain tissues make a significant contribution to the development of pathological reactivity of the body [13].

Cytokines and CNS. The size of various cytokines at the periphery prevents them from entering the brain by passive diffusion. Three main mechanisms of the penetration of cytokines into the brain have been described. The first path is through areas devoid of the BBB (the most posterior field, pineal gland, neurohypophysis, vascular organ of the terminal plate, subforonic organ, subcommissural organ).

In the second pathway, cytokines pass through the BBB with the help of specific carriers, in the region of the vessels located close to the nuclei of the hypothalamus and the blue spot. Lipopolysaccharides can also enter the third ventricle from the cerebrospinal fluid, penetrating through the ependyma and acting on the projection of the small cell nuclei of the hypothalamus.

The third route of entry of cytokines is through receptor-mediated endocytosis. Further, cytokines penetrate into deeper areas of the brain, mainly into the nuclei of the hypothalamus, hippocampus,

amigdala, and autonomic nuclei of the brainstem and appear among the activators of the stress response [13].

Cytokines can also transmit signals to the central nervous system by stimulating the vagus nerve and activating areas of the brainstem [48]. Circulating pro-inflammatory cytokines such as IL-1, IL-6, TNF are the main activators of microglial cells and astrocytes [26]. Cytokines damage CNS neurons by activating microglial cells and astrocytes [45]. Directly activated by peripheral cytokines, microglial cells and astrocytes synthesize their own pro-inflammatory cytokines, thereby causing a vicious circle. It should be noted that the interaction between microglia and astrocytes is of paramount importance in the regulation of the inflammatory process in the central nervous system and communication with neurons [31].

Inducible nitric oxide synthase. Expression of IL-1 in the brain stimulates the synthesis of nitric oxide (NO) via an inducible isoform of NO synthase (iNOS) [7]. Nitric oxide blocks the mitochondrial respiratory chain in neurons, which can cause their premature death. The neurotoxic effect of NO on microglial cells suppresses the activity of the neuroendocrine response. Nitric oxide also causes apoptosis of neurons in the hypothalamic and autonomic nuclei, which suppresses the adequate stress response in critical conditions in the form of a decrease in corticotropin-releasing hormone, adrenocorticotropic hormone, vasopressin.

In addition, at low concentrations, NO inhibits the release of catecholamines from the adrenal glands and sympathetic nerve endings, leading to a limitation of the stress response [41].

Hypoxia. Damage to the nuclei of the central nervous system during stress is of a multifactorial nature and is not limited only to the influence of cytokines and nitric oxide. An essential role in the pathogenesis of the development of pathological reactivity is played by hypoxic-ischemic brain damage, leading to a violation of the synthesis of neurotransmitters - catecholamines and acetylcholine [3, 4, 27]. Moreover, one of the most vulnerable areas of the brain is the ancient cortex - the limbic system, in which the hippocampus plays a leading role. Consequently, damage to the pyramidal cells of the hippocampus leads to a violation of the formation of the stress-response strategy [6, 23].

Conclusion. At all stages of managing the constancy of the internal environment, there is a coordinated productive interaction of neurons of the limbic, hypothalamic and noradrenergic systems. In particular, the limbic system is capable of recognizing danger, analyzing, comparing with past experience, and choosing ways to overcome a critical state. At the same time, the hypothalamic and noradrenergic systems directly modulate metabolic, immune and hemodynamic reactions.

Physiological, and – when exposed to physical stressors – pathological reactivity of the body, is directed to the initial point of balance. Pathological reactivity when exposed to physical stressors can have both reversible and destructive effects on the body. The body's response to stress is formed on the basis of incoming information from the vagus nerve, peripheral cytokines that interact with the receptors of organs surrounding the cerebral ventricles, cerebral vessels, and local formation of cytokines in the central nervous system. The blood-brain barrier plays an important role in controlling the inflammatory process in neurons and glial cells. There is ample evidence that sepsis destroys the BBB, while the entry of pro-inflammatory mediators and other neurotoxic molecules (such as urea) into the brain becomes easier. In this case, the destruction of the BBB occurs under the influence of prolonged exposure to IL-1, TNF and NO [34, 40]. Cytokines, which are one of the main triggers of the stress response, stimulate the production of inducible NO synthase and lead to damage of the nuclei of the limbic, hypothalamic, and noradrenergic systems, thereby disrupting the neuroendocrine response. Further damage to DNA neurons in the hippocampus, hypothalamus, and the nuclei of the autonomic nervous system leads to depletion of the protective stress response, which leads to a critical state of the body.

Despite the extremely important role of neuroendocrine factors in the realization of critical conditions, their significance, as well as indications and measures of influence on them, have not yet been studied in detail.

Further study of the effect of physical stressors on the neuroendocrine system can be of practical use for creating algorithms for the diagnosis and treatment of endocrinopathies in critical conditions. The concept of endocrinopathies of critical conditions in the future can become the basis for assessing the endocrine status in order to resolve the issue of the need for substitution therapy.

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