Romanova K. B., Hancheva O. V. Modern ideas about the role of the hypothalamus in the implementation of adaptation programs under stressor loads (references). Journal of Education, Health and Sport. 2022;12(2): 302-312. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2022.12.02.032
https://apcz.umk.pl/JEHS/article/view/JEHS.2022.12.02.032
https://zenodo.org/record/6819113

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 1, 2021. No. 32343. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).

Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 1 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe:Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

Received: 31.01.2022. Revised: 08.02.2022. Accepted: 28.02.2022.

UDC 616.831.4-06:616.85-009.86]-092

MODERN IDEAS ABOUT THE ROLE OF THE HYPOTHALAMUS IN THE IMPLEMENTATION OF ADAPTATION PROGRAMS UNDER STRESSOR LOADS (REFERENCES)

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Abstract

The starting point for the prevention of human disease is the study of the vital functions of a healthy organism, taking into account complex effects of external and internal factors. More often in clinical practice, doctors observe patients with advanced pathology, when the body has undergone significant changes, including at the level of systemic regulation (CNS, hypothalamus) and at the level of intercellular signaling and neuro-immune-endocrine interactions. Therefore, the basis of these changes, more often, are insignificant but permanent factors of the external or internal environment, which gradually accumulate and

disrupt the functioning of central regulatory systems. **The aim** of our study was to analyze modern sources of information that highlight current issues of the role of the hypothalamus in the development of adaptation programs during the formation of stressors. **Materials and methods:** analysis of scientific publications taken from Google Scholar databases, Web of Science, Pub Med by keywords: rats, stress reactions, adaptation, neuroendocrine regulation, neurotransmitters, hypothalamus, supraoptic nucleus, paraventricular nucleus. **Conclusions:** Thus, the analysis of scientific sources demonstrated that the main stress studies were devoted to determining the state and role of dominant systems, but there were few facts that had explained the long-term changes of the hypothalamus in regulatory systems. These issues remain unresolved and need to be studied.

Introduction. Today, many facts and clinical observations about the complex effects of chronic stress of human body. The National Institutes of Health and the U.S. Veterans Health Administration conducted a large-scale cohort study that had provided evidence of an association between post-traumatic stress disorder and cardiovascular risk, had identified mechanisms that could cause this association, and had assessed prognostic risk, cardiovascular diseases [1]. Moreover, they form a post-stress syndrome, which by itself becomes a pathogenetic mechanism of disease formation.

Rebeca Robles-García together with other researchers in 2020 demonstrated that high urbanization could increase the risk of post-traumatic stress disorder due to the concentration of poverty, limited living space, substance use and crime. Women tend to be more disadvantaged socially and economically and are more likely to be victims of collective and domestic violence than men. Accordingly, urban women are more prone to traumatic events that increase the prevalence of post-traumatic stress disorder than rural women and men in both rural and urban areas, especially those without social and family protection and support [2]. That is, even minor and indistinct stressors that act constantly and can not be overcome by man become an important etiological factor in the formation of a number of diseases.

Key words: rats; stress reactions; adaptation; neuroendocrine regulation; neurotransmitters; hypothalamus; supraoptic nucleus; paraventricular nucleus.

Analysis of research on modeling long-term social stress and its effects on the body

Without considering a rather complex question of the extent to which stressful situations cause human disease are reproduced in animals, the real situation in science is

considered to be quite justified and the fact that "To implement a defensive reaction and a" ban "on this reaction [3-4].

In the course of such modeling, it became clear that the degree of stress response and emerging damage increase significantly if the main elementary conflict is layered with additional effect that enhances the activation of the emotional apparatus. Such additional effects are the introduction of signals that warn in advance of the imminent painful blow, the impact at random in not too short periods of time, which give rise to expectations of pain, combined with anxiety and fear. The introduction is of similar importance, in addition to the main conflict, namely, inflicting pain in response to a food reaction or inflicting pain in response to a reaction by which the animal previously managed to avoid danger [5].

The reproduction of additional effect through social intragroup conflicts in animals is equally interesting - the restriction of living space, the constant transfer to new groups of animals. It is under such conditions that gastric ulcers occur with such greater constancy that they were included in the list of mandatory signs of the first emergency stage of stress syndrome [6-7].

Stress syndrome, which is realized as a nonspecific link of adaptation, may not be accompanied by the development of ulcerative lesions of the gastric mucosa, but there is no doubt that the development of such damage is one of the first and still clear manifestations of stress in the pathogenesis. Therefore, ulcerative lesions play the most important role in interpreting the mechanism of stressors [8-9].

It is known that there are three periods of stress in the dynamics of the reactions of the adrenergic and hypothalamic-pituitary-adrenal system. In the first period from the beginning of emotional pain and during 36-39 hours after its end - the level of corticosterone in plasma and organs increases 3-4 times, the heart and adrenal glands decrease 1.5-2 times, the content of catecholamines, the synthesis of labeled norepinephrine decreases in these organs, the expressed eosinopenia develops.

In the second period 39-45 hours after the end of the stress factor - the level of corticosterone in the blood plasma and organs decreases sharply and eosinophilia develops. In the third period - over the next 6-7 days, the indicators of the functional state of the adrenergic and hypothalamic-pituitary-adrenal systems are gradually approaching the initial values. Adaptive attenuation of the stress response to repeated stress is manifested not only in reducing its intensity (reduction of hormonal responses and reactions of target organs), but also in reducing the duration of these responses. Any stress is accompanied by eosinopenia

caused by an excess of corticosteroids. At the end of stress, eosinopenia not only stops, it ends with a significant increase in eosinophils, so the time from the end of the stressful situation to the peak of eosinophils, i.e. the duration of eosinopenia, is a good criterion for completion of the stress response. The shorter this period, the closer to the end of the process of adaptation to any factor, including stress. To understand this phenomenon, it should be kept in mind that in the process of adaptation, along with the extinction of the stress response itself, a kind of decrease in sensitivity develops - desensitization to stress mediators and hormones [10].

Obviously, the most likely cause of such high resistance to stressors is a decrease in the number of beta-adrenoceptors and their affinity for catecholamines, i.e. the same phenomenon that underlies the adaptive effect of desensitization. To acquire the process of adaptation or genetically determined reduction of adrenoreactivity is a powerful factor against stress protection [11-12].

In this regard, a possible mechanism of desensitization is of interest. There are studies that link the phenomenon of desensitization with changes in the lipid bilayer of cell membranes of neurons and executive organs, with changes in the lipid microenvironment of adrenoceptors under repeated stress. During desensitization in the membranes is the destruction of phosphatidylcholine and the accumulation of its decomposition products - lysophosphatidylcholine and arachidonic acid. Phospholipase A inhibitor blocks this process and makes it impossible to desensitize in vivo and in vitro in the brain and heart [13-14].

One of the important mechanisms of adaptation to stressful environmental situations is the activation of central regulatory mechanisms, which under the action of emotional pain and other similar stimuli inhibit the release factors and as a result of the release of corticosterone and catecholamines. The system of inhibitory neurons synthesizes and isolates inhibitory mediators in the brain: gamma-aminobutyric acid (GABA), dopamine, serotonin, glycine and other inhibitory peptides [14-15].

Regulatory systems of adenine nucleotides are equally important at the periphery, prostaglandins, antioxidant systems, which act as modulators, can limit the excessive effects of catecholamines and other factors, thus becoming the basis of desensitization and prevent stressors [16].

Materials and methods: analysis of scientific publications taken from Google Scholar databases, Web of Science, PubMed by keywords: rats, stress reactions, adaptation, neuroendocrine regulation, neurotransmitters, hypothalamus, supraoptic nucleus, paraventricular nucleus.

Key experimental studies of the state of hypothalamic neurons in stress models

An experimental study of the state of hypothalamic PVA neurons in hypertension caused by stress revealed neuroinflammation in the structure of the nucleus. The authors believe that increased intrusion of peripheral immune cells into PCOS may be associated with increased regulation of chemokines and activation of microglia cells. Cytokine imbalance was observed due to the fact that stress increased the expression of the protein of pro-inflammatory cytokines IL-6 and IL-17 and decreased the expression of anti-inflammatory cytokines TGF-ß and IL-10 in PVN [17].

A group of researchers together with Naoya Kataoka in 2020 in a study of Physiological responses to Psychological stress revealed a central major neural pathway in rats that controls autonomic and behavioral responses to stress by connecting corticolimbic stress chains to the hypothalamus. Psychosocial stress signals from emotion-related areas of the forebrain activated the VGLUT1-positive glutamatergic pathway from the dorsal leg cortex and dorsal tectonitis (DP/DTT) to the dorsomedial hypothalamus (DMH). According to them, this pathway mediates the behavior of avoiding Psychosocial stressors [18].

Another team of scientists has shown that acute inhibitory stress (RS) caused the activation of neurons in the supraoptic nucleus of the hypothalamus (SON). The authors showed that pre-treatment of SON with cobalt chloride reduced blood pressure and heart rate, which were previously increased due to stress. In addition, previous treatment with SON $CoCl_2$ reduced the stress-induced increase in corticosterone and oxytocin without affecting plasma vasopressin levels, indicating its important role in stress-induced neuroendocrine responses. The results showed that SON was an important component of the neural pathway that controled autonomic, neuroendocrine and behavioral responses induced by acute inhibitory stress [19].

Researchers at the Department of Pharmacology at the Ribeiran Preto School of Medicine, University of São Paulo, investigated the involvement of nitrergic neurotransmission in the paraventricular nucleus of the hypothalamus (PVN) in modulating local neuronal activation, autonomic and neuroendocrine responses in behavioral and sequelae. They showed that bilateral microinjections of the selective nitric oxide synthase inhibitor (nNOS) Nw-propyl-L-arginine (NPLA) or the carboxy-PTIO absorber in PVN lower blood pressure and increased heart rate, as well as reduced skin temperature, caused by restrain-stress. The researchers concluded that nitrengic neurotransmission PVN, which acted through nNOS activation, had a beneficial effect on the autonomic response to acute

limitation and delayed emotional effects of stress, and confirmed the opinion of many researchers on the important role of local nitrenergic neurotransmission [20].

Thus, present studies of different mechanisms of stress models demonstrate a key role in the implementation of autonomic responses needed to overcome stress, hypothalamic structures, among which the most important are large-cell neurons PVA and SOY. It is necessary to note the works devoted to the elimination of the role of the nitritergic system in the development of stress reactions. A special attention is paid to neuronal nitric oxide synthase without removing all other components of the isoform profile.

The hypothalamus, as the ventral part of the diencephalic region of the brain, is a complex structure that contains a complex of nuclear formations and is closely related to different levels of the CNS and pituitary gland. It is an important focal point for the nervous and endocrine systems [21].

It should be noted that the peculiarity of hypothalamic integrating neurons, in contrast to neurons in other parts of the CNS, is a dual property - they are sensitive to the action of neurotransmitters released in the presynaptic terminals; and to the effect of environmental factors of an individual neuron: temperature, glucose levels, neuropeptides, neurotransmitters, gas transmitters and other biologically active compounds [22-23].

Today, many scientists have proven that the hypothalamus is considered to be an important substrate for the integration of various emotional and behavioral responses and their coordination with hemodynamic and cardiovascular relationships.

Studies concerning the connection between visceromotor and somatomotor manifestations of holistic somato-vegetative reactions of emotional and behavioral type, associated with different structures of the hypothalamus, have been conducted in some laboratories. The researchers showed that irritation in acute experiments of hypothalamic structures, which in the same animals caused in previous chronic research series of food or protective behavioral responses, led to characteristic patterns of cardiovascular responses to each type of behavioral response. Correlation of cardiovascular reactions with emotional and behavioral manifestations that occur during stimulation of the hypothalamic zones associated with the sympathetic ANS [24-25].

In other studies, it was shown that cats developed excitement, aggressive behavior, and increased blood pressure and blood flow in the ascending aorta, superior mesenteric artery, and external vertebrae after irritation of the gray matter of the midbrain. Cardiovascular changes were expressed during animal fights by tachycardia, a sharp and rapid

increase in muscle tone associated with increased muscle activity. Visceral vasoconstriction and vasoconstriction in inactive muscles occurred simultaneously. The authors note that in animals, in the preconfrontation period, during the development of an exclusively emotional state of rage-fear, cardiovascular shifts were characterized by reduced cardiac output, decreased blood flow in the iliac artery (muscular circulation) and some reduction in blood pressure due to decreased cardiac output and changes in peripheral vascular resistance. The results of their research indicate that exclusively emotional tension is characterized by muscle vasoconstriction and sympathetic cholinergic muscle vasodilation, which occurs when protective areas of the hypothalamus are irritated or naturally excited (nuclei associated with the centers of the sympathetic nervous system). The authors' research on the steady increase in blood pressure with repeated stimulation of the emotional hypothalamus deserves great deal of attention. In a chronic experiment, prolonged daily irritation of the protective zone of the hypothalamus caused a gradual increase in blood pressure. The authors believe that with repeated mental stress, chronic excitation of the protective zone of the hypothalamus are trigger mechanisms for the genesis of chronic hypotension in humans [26].

There are enough facts about neurogenic alpha-adrenergic cerebral vasoconstriction in irritation of the posterolateral and supraoptic areas of the hypothalamus and mild cholinergic vasodilation in irritation of its preoptic area [27].

Among the works devoted to the study of the effect of the hypothalamus on regional hemodynamics, a research on the hypothalamic regulation of coronary circulation is of particular importance. Research on this issue is important because the excitation of "emotional areas" of the hypothalamus under emotional stress are accompanied by abrupt changes in coronary tone, very often coronary spasm and myocardial infarction becomes a tragic ending of the emotional storm that arises in the hypothalamus [28-29].

All these groups of studies suggest that autonomic and partially cardiovascular reactions that occur in irritated areas of the hypothalamus associated with the sympathetic ANS are a component of different types of emotional and behavioral responses to stress. Researchers argue that the hypothalamus is a key agent in the development of specific changes in regional blood circulation and cardiac activity under the influence of stressors [30-31].

Conclusions: Thus, the analysis of scientific sources showed that the main research on stress is to determine the state and role the heart, brain, adrenal glands and liver as its dominant systems, but there are few facts that explain long-term changes in regulatory

systems of hypothalamus. There is a lack of evidence on the connection between the state of hypothalamic neurons, which act as a key conductor of stress response. There is no clear concept of the role of long-term social stress with limited living space on the nature of the isoform profile of the enzyme NOS – an important component of the gas-transmitter system of nitric oxide. These issues remain unresolved and need to be studied.

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