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# THE INFLUENCE OF CHANGES IN THE ACTIVITY OF THE DOPAMINERGIC AND SEROTONERGIC SYSTEMS OF THE HYPOTHALAMUS ON THE AMOUNT OF MONOAMINES AND HORMONES AGAINST THE BACKGROUND OF EMOTIONAL STRESS

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**Abstract.** The article presents the results of research conducted for the purpose of studying to study the influence of chronic emotional stress (CES) on the activity of the dopaminergic (DA-ergic) and serotonergic (5-HT-ergic) systems of the hypothalamus and against this background, changes in the amount of monoamines (MA), somatostatin (ST) and hormones. The rats were subjected to CES with an electrical shock lasting 30 minutes. Studies show that after all days of exposure to stress, the concentrations of ST, dopamine (DA) and noradrenaline (NA) in the hypothalamus and blood increase sharply. In contrast, the levels of serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) are significantly reduced. The restructuring and content of ST, DA and 5-HT and their metabolism occurs in a similar way throughout the body. Disruption of the mechanism of interaction between the DA-ergic and 5-HT-ergic systems in the hypothalamus and blood against the background of stress leads to a change in the active biochemical reciprocity between these systems. Under the stress, the DA-ergic and ST-ergic functional systems predominate over the 5-HT-ergic functional system. The DA/5-HT ratio, reflecting the functional interaction of these MA, increases in the dynamics of stressful functional development of the body. This once again proves the superiority of the activity of the DA-ergic system over the 5-HT-ergic system in the process of CES. During stress, DA, ST and NA have synergistic properties. These neurotransmitters act antagonistically with 5-HT.As a result of these changes, a hormonal imbalance in the body occurs, the activity of cortisol, adrenocorticotropic hormone (ACTH) and estradiol increases, and the activity of thyroid hormones and somatotropin (STH), prolactin (PRL) decreases. Thus, changes in the activities of the DA-ergic, ST-ergic and 5-HT-ergic systems of the hypothalamus against the background of stress, depending on its duration, lead to an imbalance of MA, ST and hormones. Therefore, studying the pathogenetic mechanisms of this system under extreme conditions and identifying the role of regulatory mechanisms may allow solving a number of different practical issues.

***Keywords:*** *Emotional stress, hipotalamus, monoamine, neuropeptide, hormone*.

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## 1. Introduction

Modern scientific and technological progress, acceleration and urbanization, a wide flow of information, an increase in the emotional level, renewal and increase in needs, the continuation of long-term conflicts in various conditions and a number of stimuli (endo- and exogenous factors) create optimal conditions for a person to fall into stress. Many external environmental factors, having a negative impact on various functional systems of the body, cause certain pathophysiological changes. Therefore, in medicine, from the point of view of public health, stress is considered as an urgent problem (Alekseeva *et al.*, 2019; Engert *et al*., 2019; Filaretova, 2010; Ismayilov *et al*., 2023; Kotiyev *et al.*, 2022) problem of stress has become even more acute in recent years. So, stressors of various etiologies, affecting the body, change homeostasis and become the leading causes of many diseases (Fedotov, 2009; Ismayilov *et al.*, 2019a; 2023; Stefanaki *et al.*, 2018). Authors conducting research in this direction have shown that the main reason for the unsuccessful course of various diseases is a prolonged and intense background of emotional stress (Deak *et al.,* 2017; Engert *et al*., 2019; Filaretova, 2010; Kotiyev *et al.*, 2022).

It has been shown that there is a close relationship between emotional stress and behavioral, hormonal and other physiological processes (Alekseeva *et al*., 2019; Engert *et al.*, 2019; Ismayilov *et al.*, 2023; Kubasov, 2014). However, the sufficient complexity of the neurophysiological and neuroendocrine mechanisms that form the basis of this relationship and the fact that many questions still remain unanswered, make it necessary to conduct more in-depth research in this direction (Deak *et al*., 2017; Engert *et al*., 2019; Korneva *et al*., 2017; Ugryumov, 1999; Korneva *et al*., 2017).

Under the influence of prolonged and intense strong negative stress load, changes of various nature occur in many physiological processes. Such changes cause endocrine disorders (Ismailov *et al.*, 2019b; 2023) and nervous dysfunctions (Alekseeva *et al*., 2019; Marsland *et al.*, 2017; Veiga-Fernandes & Artis, 2018). Therefore, the study of the mechanisms of regulation of multifaceted functions of the body and their interaction remains one of the most pressing issues for science. And also, the study of the pathogenesis of changes caused by disruption of the interaction of the MA-ergic and peptidergic systems of the body in various functional systems under conditions of emotional stress remains one of the fundamental problems of modern biomedicine.

The purpose of the study was to study changes in the activities of the DA-ergic, ST-ergic and 5-HT-ergic systems of the rat hypothalamus depending on the conditions of CES and against this background, a change in the nature of the relationship between monoamines, neuropeptides and hormones.

## 2. Materials and methods

The experiments were carried out on 40 female Wistar rats weighing 250±8g. The animals were kept in a vivarium at a constant temperature of 22-24°C, with the lighting system regulated in accordance with sanitary and hygienic rules in standard laboratory conditions in special cages measuring 75x40x40 cm containing 8 animals in each cage.

The animals were fed with a generally accepted standard diet and a constant supply of water. During the experiments, the principle of protecting animals used for experiments and other scientific purposes (Declaration of the International Bioethics Committee of the European Union, Strasbourg, March 18, 1986) and the “rules of conduct with experimental animals" adopted by the local bioethics commission of the AMU (protocol №1, 03.09.20) were strictly observed. Before the main experiments, the animals were adapted to the experiments for 3-4 days. In order to exclude hormonal changes during the studies, material was taken from rats in the diestrus phase.

In the experiments, the rats were divided into 5 groups. The rats of the first group were in an intact (normal) state and their obtained results were estimated as 100%. Rats of each subsequent group - the 2nd group - for 3 days, the 3rd group - for 6 days, the 4th group - for 9 days, the 5th group - for 12 days - were subjected to CES electric current lasting 30 minutes.

To supply electric current to animals, cages with ventilation and floor covering made of steel rod measuring 30x30x40 cm were used. The animals were induced into a state of stress using an ES-50-1 electro stimulator (Ukraine) with a special automatic regulator. The machine regulates the frequency and duration of stimulation. In the experiment, animals were subjected to stress with a power of 30W in the mode of one minute of stimulation and one minute of pause (Johnson et al., 2019). The experiment was conducted daily for 30 minutes for 3-6-9-12 days. One day after the end of the experiment; the animals were decapitated using anesthesia - 5% chloralhedran, which was injected into the abdominal cavity in accordance with body weight at a dose of 25 mg/100g.

The amount of studied MA in tissues and blood was determined by a universal fluorimetric biochemical method (Kogan & Nechaev, 1970). This method allows to simultaneously determine the amount of DA, NA, 5-HT, 5-HIAA in the studied tissue sample (hypothalamus), as well as the amount of DA and 5-HT in whole blood. Fluorescence intensity was measured on a Hitachi MPF-4 spectrofluorimeter (Japan). The concentration of ST (also in tissues), PRL, STH, ACTH, thyroid-stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3) and estradiol in the blood was determined using special radioimmunological kits on a "Packard" automatic spectrometer (USA) with a special counting system.

The obtained digital data were statistically processed in a Microsoft EXCEL-2016 spreadsheet (Yunkerov & Grigoriev, 2002). The reliability coefficient of intergroup differences was determined using the Fisher-Student table.

## 2. Results and discussions

The results of the conducted studies show that, based on experimentally created chronic stress, drastic changes occur in the body. First of all, it is characterized by changes in the hypothalamic MA-ergic systems. In particular, this occurs due to deviations in the activity of catecholamines and indolamines. Thus, compared with the norm (in the groups receiving electrical stimulation), the amount of DA in the hypothalamus in rats subjected to stress increased by 36,1%, $p<0,05$ on the 3rd day of chronic stress and by 46,5%, $p<0,05$ on the 6th day (Figure 1). Compared with the norm on the 9th day, the amount of DA in the hypothalamus increases by 62,4%, $p<0.05$ and this increase in its amount remains high until the end of the experiment. Therefore, the amount of this amine we are studying in the hypothalamus on the 12th day of the experiment exceeds the norm by 61%, $p<0,05$). During the entire experiment, the increase in the amount of DA in the hypothalamus exceeds the norm by an average of 51,2%, $p<0,05$ (Figure 1).

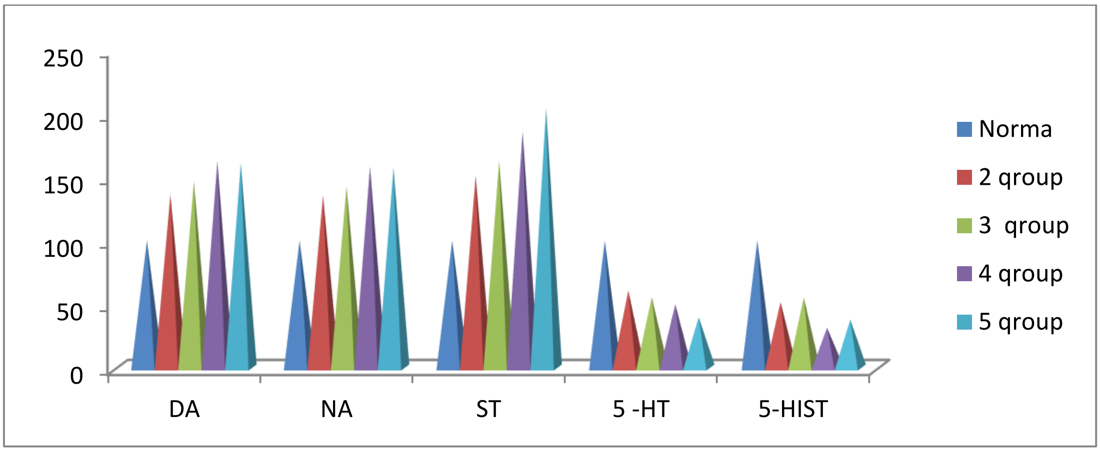


**Figure 1.** Changes in the amount of monoamines and somatostatin in the hypothalamus ofrats under the influence of chronic emotional stress (%)

Similar results are obtained for the amount of NA in the hypothalamus. Thus, compared with the norm, as a result of exposure to chronic emotional stress, its amount in the hypothalamus increases for each group by 35,5%-42,8%, 58,4%, 57,4%, p<0,05 (Figure 1). During the entire experiment, the increase in the amount of NA in the hypothalamus exceeded the norm by an average of 48,2%.

The obtained data on the amount of ST corresponded to the data on the activity of MA in the hypothalamus. Thus, compared with the norm, the number of ST in the hypothalamus in rats exposed to stress increased by 50,81%, p<0,05 on the 3rd day of chronic stress and by 62,5% on the 6th day (Figure 1). The amount of ST in the hypothalamus increased by 85,8%, p<0,001, compared to normal animals on the 9th day of exposure to the stress factor and the increase in this level continued in the following days of chronic stress exposure. Thus, on the 12th day of stress exposure, this amount exceeded the control group by 104%, p<0,001. During the entire experiment, the increase in the amount of this neuropeptide in the hypothalamus exceeded the norm by an average of 75,5%.

On the contrary, compared to the norm, the amount of 5-HT in the hypothalamus against the background of emotional stress decreases by 39,3%, p<0,05 on the 3rd day and by 44,6% on the 6th day. However, as a result of the duration of stress, the amount of 5-HT in the hypothalamus, compared to the control group, on the 9th and 12th days, respectively, decreased by 50,2% and 60,4%, p<0,05 (Figure 1). It should also be noted that along with the decrease in 5-HT activity in the hypothalamus, the amount of its final product 5-HIAA also decreases. Therefore, the amount of 5-HIAA in the hypothalamus on the 3rd and 6th days decreased by 48,5-44,8%, p<0,05 respectively, its amount in comparison with the control group on the 9th and 12th days decreased by 68,6-62,3%, p<0,05 (Figure 1). Along with this, under the influence of emotional stress, compared to the norm, the amount of DA in the blood increased accordingly by 44,6%-52,8%-59,0%-68,0%, p<0,05 per day. Under stress, the increase in DA activity in the blood averaged 56,6%, p<0,05. On the contrary, the amount of 5-HT in the blood compared to the norm decreased by 39,4%-53,3%-60,5%-68,8%, p<0,05 (Figure 2).

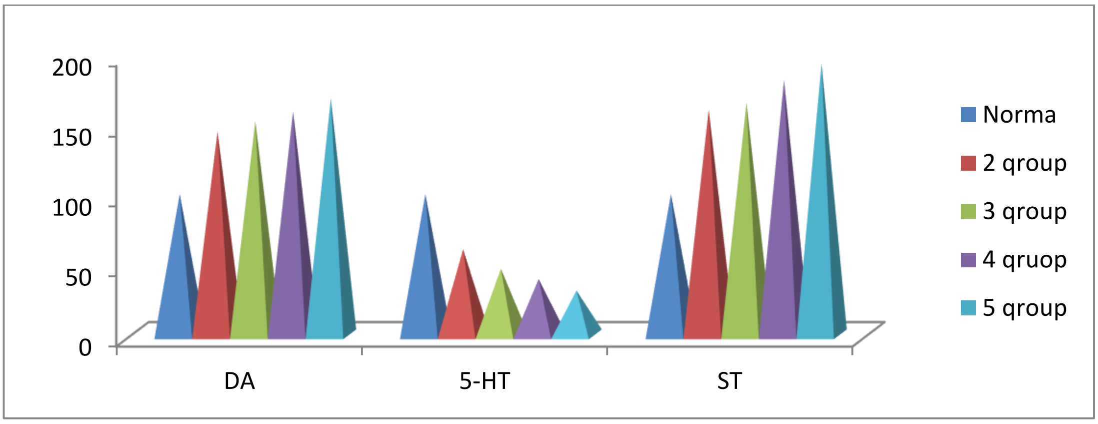


**Figure 2.** Changes in the amount of monoamines and somatostatin in blood of rats under the influence of chronic emotional stress (%)

Against the background of chronic stress, the activity of 5-HT in the blood decreases by an average of 55,2%, $p<0,05$. The increase in the amount of ST in the hypothalamus under the influence of a chronic stress factor also affected its secretion into the blood. Thus, the activity of ST in the blood as a result of the impact of 3-day chronic stress was 161,4%, $p<0,001$ higher than the norm. At the same time, this level under the influence of chronic stress after 6 days, increasing, was increased by 165,3%, $p<0,001$. The increase in stress exposure after the 9th and 12th days was 181,4% and 193,3%, $p<0,001$ respectively (Figure 2). During stress, the increase in ST activity in the blood averaged 137,4%, $p<0,001$.

The obtained results show that with increasing duration of stress, the change in activity between markers becomes more abrupt. Under these conditions, the increase in the DA/5-HT ratio, indicating a functional relationship of MA, confirms the advantage of the DA-ergic system over 5-HT-ergic activity. Under stress, the correlation coefficient between DA and 5-HT increases sharply, but in intact animals this coefficient decreases sharply. The reason for this is the increase in SA-ergic and decrease in 5-HT-ergic tone in the chain of MA-ergic regulation of the hypothalamus under the influence of chronic stress. Under the influence of chronic stress in parts of the brain, in particular in the hypothalamus, as a result of disruption of ergic functions, the relationship between neurotransmitters is disrupted and if you look even deeper, the biochemical balance between catecholamines and indolamines is directed in the opposite direction (Gromova, 1979).

As a result of the disruption of the activities of MA- and ST-ergic functional systems in stressed organisms, the processes of synthesis of PRL and STH from the tropic cells of the adenohypophysis and their secretion into the blood slow down. Thus, the amount of STH due to stress decreases by days and accordingly is 26,8-35,8-51,1-59,2%, $p<0,05$ (Figure 3).

Similar patterns are observed in the amount of PRL in the blood. Compared with the control group, its amount on the 3rd and 6th days decreases by 39,2%-48,6%, $p<0,05$ and on the 9th and 12th days by 55,1%-60,3%, $p<0,001$ (Figure 3). On the contrary, compared to the norm, the ACTH level increases in all groups. Under the influence of stress, its amount increases compared to the norm on the 3rd and 6th days of the experiment by 135,0%-156,9%, $P<0.001$ and on the 9th and 12th days by 187,2%-199,2%, $P<0.001$. Similar patterns are observed in the level of cortisol in the blood. Its level in all groups was sharply increased. This increase is above the norm by 133,7%-160,0%, -196,0%-210,0%, P<0,001 (Figure 3).

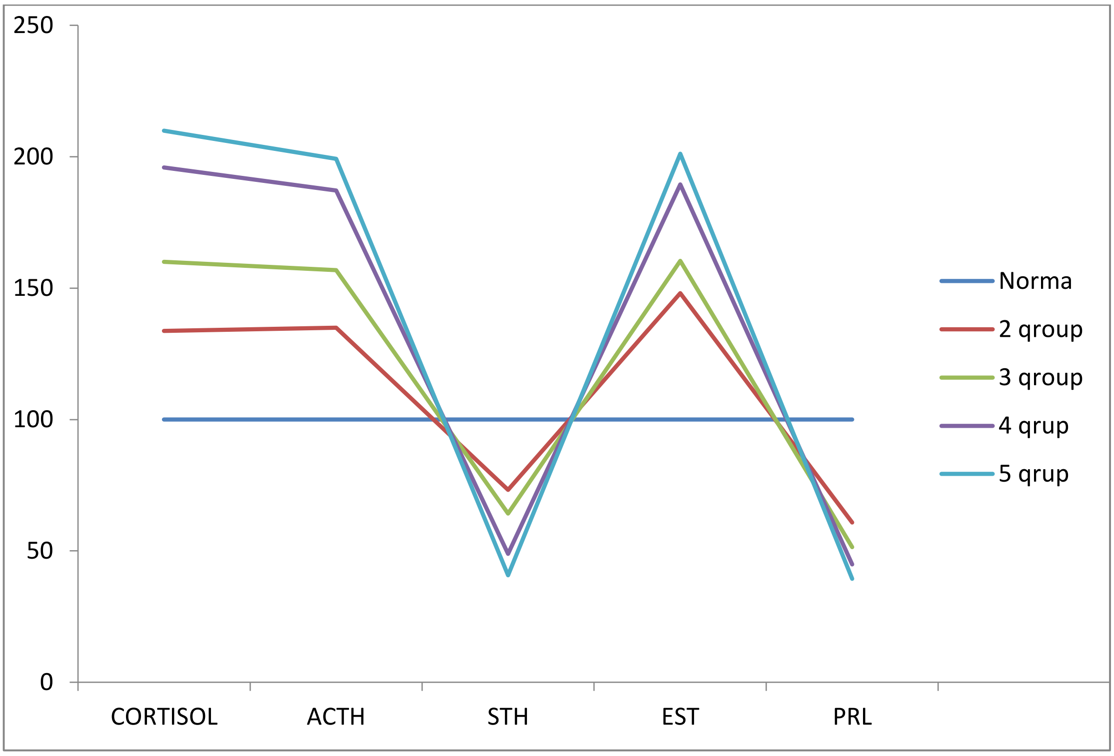


**Figure 3.** Changes in the amount of hormones in blood in rats under the influence of chronic emotional stress (%)

Certain patterns are also observed in the thyroid status of the adenohypophysis-thyroid gland. Against this background, the level of TSH in the blood in all groups increases sharply (161,5 - 170,2 - 180,3 - 236,4%, $p < 0,001$). The level of T4 compared to the norm under the influence of stress decreased accordingly by days by 37,6% - 55,5% - 59,8% - 67,8%, $p < 0,05$. The level of T3 in the blood compared to the norm decreases by 43,9% - 42,9% - 52,6% - 53,4%, $p< 0,05$. This change in the level of thyroid hormones, in turn, leads to an increase in the secretory activity of pituitary thyrotropocytes based on the principle of feedback. In groups of rats exposed to stress, the functioning of the pituitary-thyroid system can thus be explained by a weakening of the hormone-synthesizing activity of the thyroid gland during chronic stress, which leads to its functional insufficiency. The low correlation between T3 and PRL during stress confirms the synergism of these hormones during stress. It is interesting that the noticeable weakening of this correlation during stress is due to the fact that as a result of neurogenic stress, the regulatory mechanism between the thyroid gland and the pituitary gland is disrupted. Estradiol activity in the blood increases sharply in all groups (Figure 2).

Thus, as a result of chronic emotional stimulation by electric current in the experiment, the fear factor and pain reactions disrupt the physiological functions of the hypothalamic-pituitary system, in particular, as a result of disruption of the function of the anterior lobe of the adenohypophysis and the thyroid gland, a slowdown in the production of hormones occurs.

## 2. Conclusion

The results show that, depending on the duration of the CES, the disruption of the mechanisms of the relationship between the MA-ergic systems and the active biochemical reciprocity existing between them lead to deviations from the norm in the activities of lactotropic, stress and thyroid hormones in the blood (Ismailov *et al*., 2019; Salimli *et al*., 2022).

Under the influence of stress, the activity of ST, DA and NA in the hypothalamus and blood has the same direction and a synergistic effect is possible. However, during stress, the mechanism of the functional relationship between ST, DA and 5-HT is disrupted. Under these conditions, the dominance of the ST-ergic and DA-ergic systems over the 5-HT-ergic system causes hormonal imbalance. The results obtained show that neurohormonal regulation of the body is an integrative process and in this regulation, neuropeptides, neurotransmitters and hormones of the endocrine system, exerting a mutual effect, regulate the physiological functions of the body. However, as a result of exposure to stress, very serious changes occur in some aspects of this integrative connection (Deak *et al*., 2017; Engert *et al*., 2019; Filaretova, 2010; Kotiyev *et al.*, 2022).

Thus, in normal organisms there are mechanisms with a fine dialectical dependence, which have both an activating and an inhibitory effect on the stress factor. Their coordination reaction allows the organism to get out of an extreme situation. However, under the influence of chronicemotional stress, violations of the biochemical reciprocity between monoaminesin the hypothalamus and blood and the activity of the somatostatic functional system lead to a deviation of the hormonal reactivity of the body from the norm. Therefore, the study of the relationship between neurotransmitters and hormones, as well as their pathogenetic mechanisms and the identification of the role of these regulatory mechanisms in extreme conditions make it possible to findsolutions to variouspracticalissues.

Thus, the obtained results can become a theoretical and practical basis for a targeted search for ways to prevent stress-related disorders of homeostasis in the organism.

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