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MODULATION OF MONOAMINERGIC NEUROTRANSMISSION RESTORES MNESTIC IMPAIRMENTS IN RATS WITH CHRONIC UNPREDICTABLE STRESS

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The purpose of the study was to investigate the expression of learning and memory processes in rats in chronic unpredictable stress dynamics in conditions of serotoninergic, dopaminergic and adrenergic neurotransmitter systems activity modulation. Experimental studies were performed on the model of chronic unpredictable stress on Wistar rats with previously induced the serotoninergic, dopaminergic and noradrenergic neurotransmitter systems activity activation and suppression. Animals' ability to learn and their short- and long-term memory expression were determined in the dynamics of used model, The data obtained confirm the expressed mnestic disorders development in rats during the chronic unpredictable stress manifested by deterioration of learning, memory engrams formation and preservation. Mnestic disorders were shown to be developed from the 1st day of chronic unpredictable stress induction, progressed in its dynamics and were maximally expressed from the 14th day of the trial. Serotonin, dopamine and adrenergic neurotransmission suppression starting from the 7th day of the trial significantly impaired rats learning and short- and long-term memory and their activation on 21st day of the trial resulted in mnestic dysfunctions normalization. The authors stressed on monoaminergic neurotransmission functional activity accounting while analyzing the persons cognitive capabilities in chronic stress conditions. The data obtained are experimental evidence of monoaminergic neurotransmission activation clinical effects testing reasonability in chronic stress conditions while performing the treatment regimens for mnestic disorders pathogenetic therapy in patients with chronic unpredictable stress.

Key words: chronic unpredictable stress, ischemia, monoaminergic neurotransmission, mnestic disorders, conditioned reflexes, learning, memory, pathophysiological mechanisms, sanogenetic mechanisms.

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МОДУЛЯЦІЯ МОНОАМІНЕРГІЧНОЇ НЕЙРОПЕРЕДАЧІ ВІДНОВЛЮЄ МНЕСТИЧНІ ПОРУШЕННЯ ЗА УМОВ ХРОНІЧНОГО НЕПЕРЕДБАЧУВАНОГО СТРЕСУ В ЩУРІВ

Метою дослідження було вивчення вираженості процесів навчання та пам'яті у щурів в динаміці відтворення хронічного непередбачуваного стресу за умов модуляції активності серотонінергічної, дофамінергічної та адренергічної нейромедіаторних систем. Експериментальні дослідження проводили на моделі непередбачуваного хронічного стресу на щурах лінії Вістар, в яких завчасно сприяли активації та пригніченню активності серотонінергічної, дофамінергічної та норадренергічної нейромедіаторних систем. В динаміці означених модельних умов у щурів визначали здатність до навчання, а також вираженість коротко- та довгочасної пам'яті. Отримані дані свідчать про розвиток в динаміці хронічного непередбачуваного стресу мнестичних розладів у вигляді погіршення процесів навчання, а також формування та збереження енграми пам'яті. Мнестичні порушення формуються з 1-ї доби відтворення хронічного непередбачуваного стресу, прогресують в його динамівці та є максимально вираженими, починаючи з 14-ї доби досліду. Пригнічення активності серотонін-, дофамін- та адренергічної нейротрансмісії, починаючи з 7 доби досліду, суттєво погіршувало здатність щурів до навчання та функціонування коротко- та довготривалої пам'яті, а її активація на 21-й добі сприяли відновленню мнестичних функцій. Автори наголошують на важливості урахування функціональної активності моноамінергічної нейротрансмісії при аналізі когнітивних можливостей організму за умов хронічного стресового впливу. Отримані дані є експериментальним доказом доцільності тестування клінічних ефектів активації моноамінергічної нейротрансмісії за умов хронічного стресового впливу при складанні схем патогенетичнї терапії мнестичних розладів у хворих з хронічним стресом.

Ключові слова: хронічний непередбачуваний стрес, ішемія, моноамінергічна нейропередача, мнестичні порушення, умовні рефлекси, навчання, пам'ять, патофізіологічні механізми, саногенетичні механізми.

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Under the influence of any environmental factor, a general adaptive response is initiated in the human body which fundamental mechanisms were firstly established by G. Selye and later thoroughly studied by other specialists [3, 12, 15]. Today, the stress response has significantly changed all its main characteristics and parameters: the nature of the stress upshot from acute short-term irritation has acquired a chronic character which significantly changed the nature of both adaptive and/or compensatory reactions manifestation in a biological organism in response to environmental factors, exogenous and endogenous factors of excessive intensity influence [3, 7]. Stress effects "chronization", new etiological factors, the impact of polystress factors on human body as opposed to mainly monostress effect that was previously registered, frequent cases of body's response complete desynchronization, of regulatory stress-limiting systems functional activity disorder, frequent cases of stress response comorbidity with pathological

conditions and/or diseases initiated by vital systems and organs of the body functional activity disruption – all of the abovementioned is only the tip of the iceberg of new aspects in problem of stress [3, 8, 9, 15].

We believe important to have a clear understanding of biological organism adaptive mechanisms in response to stressor impact, since in recent decades, a significant amount of clinical material proved that a stress factor is not so much the adaptive response initiator as a "trigger" for certain diseases initiation caused by adaptation mechanisms breakdown and compensatory/regulatory mechanisms failure at the energetical, biochemical, morphological, physiological, biological and even psychological levels [9, 15]. This shows the importance of a thorough study of general adaptive stress-induced reaction mechanisms with attempts to establish a number of factors that can enhance the stress-limiting systems activity and prevent or even limit the organisms' systemic response toward the stress factor influence in conditions of regulatory organs and organ systems dysfunction.

Chronic stress, unfortunately, has long become an integral part of contemporary life [3, 12]. Additional stressful moments at work or in the workplace, during training, in the dynamics of the enemy's more than three-year military aggression against our country, from one side, overweight the human organisms by stress-induced consequences, and, from the other side, determine the activity of the body's main physiological systems, thereby changing the person's ability to maintain homeostatic indexes [9].

In conditions of constant influence of a stressor stimulus of insignificant intensity, its summation occurs – this is a physiological mechanism, and our present life significantly changes the characteristics of stress impact on the body – such a daily human condition is characterized as one that is realized as a result of chronic unpredictable stress (CUS) influence [8, 9]. Such a situation allowed us to use the CUS model to determine the main stress-induced disorders of the body's physiological systems, with efforts to reveal their entire pathophysiological mechanisms. Motor activity limitation, the emotional behavior of animals changes due to depressive conditions formation were proved [1]. Analyzing these animals' changes of behavior in conditions of the applied model we decided to check them from the point of view of cognitive dysfunctions probable development throughout the chronic stress dynamics, since both the hypolocomotor activity and animals' emotions determine the expression of excitative processes in the body, which mutual appearance, in turn, has a significant impact on the processes of learning and memory [11].

The purpose of the study was to investigate the expression of learning and memory processes in rats in chronic unpredictable stress dynamics in conditions of serotoninergic, dopaminergic and adrenergic neurotransmitter systems activity modulation.

Materials and methods. Experimental studies were performed on 125 white mature male Wistar rats during 2022–2023 based on the scientific laboratory of the Human Anatomy Department of Odesa National Medical University (ONMedU) and the experimental biological clinic (vivarium) of ONMedU. The animals were kept in standard vivarium conditions. Experimental animals keeping and manipulation was done in accordance with the "General Ethical Principles of Animal Experiments" adopted by the Fifth National Congress on Bioethics (Kyiv, 2013) and was guided by the recommendations of the European Convention for the Protection of Vertebrate Animals for Experimental and Other Scientific Purposes (Strasbourg, 1985) and guidelines of the State Pharmacological Center of the Ministry of Health of Ukraine on "Preclinical studies of drugs" (2001) as well as rules of humane treatment of experimental animals.

L-tryptophan (LT; intravenously (i.v.) 100 mg/kg, during 14 days) and parachlorophenylalanine (PCPA; i.v.; 300 mg/kg, during 3 days), correspondingly, we used to activate and inhibit the activity of the serotoninergic neurotransmitter system (NS). The dopaminergic NS activity both activation and suppression were achieved via the use of deprenyl (DP; intraperitoneally (i.p.); 3 mg/kg, during 14 days) and haloperidol (HP; i.p.; 2.5 mg/kg, during 3 days), respectively. Ludiomil (LD; i.p.; 20 mg/kg, during 14 days) and α-methyl-paratyrosine MP; i.p.; 80 mg/kg, during 3 days) were used for noradrenergic NS activity activation and inhibition [14].

The rats were randomized as following: group 1 – control (falsely stressed, n=7); group 2 – 11 rats with CUS; group 3 – LT+control (n=9); group 4 – LT+ CUS (n=9); group 5 – PCPA+control (n=9); group 6 – PCPA+ CUS (n=9); group 7 – DP+control (n=9); group 8 – DP+ CUS (n=9); group 9 – HP+control (n=9); group 10 – HP+ CUS (n=9); group 11 – LD+control (n=9); group 12 – LD+ CUS (n=9); group 13 – MP+control (n=9); group 14 – MP+ CUS (n=9).

After the NS activation/inhibition in rats, CUS was reproduced according to generally accepted method during 4 weeks by changing the nature of stressor and time of its application [10]. Stressor stimuli were applied to rats once a day at different time intervals from 08.00 to 18.00. Control rats were handled during 20-30 sec and then returned to cages. The model used peculiarity is the unpredictable nature of stress application for each 7 days [1, 10].

1 day, 7, 14 and 21 days after the end of CUS induction in rats, the severity of the learning and memory processes was determined by conditioned active avoidance reactions (CAAR) development in them by giving the animals a conditioned (CS) and unconditioned stimuli (US) [13]. The "preservation" index was calculated as an integrative index of mnestic functions expression [9].

The obtained results were statistically analysed using the Bonferroni parametric criterion. The minimum statistical significance threshold was set at $p<0.05$.

Results of the study and their discussion. The number of CS and US combinations required for CAAR occurrence in rats 24 hrs after the trial start was 27.2±2.6 which corresponded to the same index in the control group of animals (Table 1). In stressed rats with early serotonin and dopaminergic NS activity inhibition the studied index was 34.2±3.1 and 33.8±2.9, respectively, which was 43.7 % and 42.0 % higher compared to corresponding control index, as well as 25.8 % and 24.3 % higher, respectively, vs the similar index in rats with CUS (in all cases $p<0.05$). The value of the studied index in the rest experimental groups was comparable to similar control index ($p>0.05$).

Table 1

Changes in learning and memory processes in rats in chronic unpredictable stress dynamics in conditions of serotoninergic, dopaminergic, and adrenergic neurotransmitter systems activity modulation

Experimental groups	Number of CS and US stimuli combinations required for CAAR (M±m)		
	Training	Short-term memory	Long-term memory
1 day after CUS initiation			
Control, n=7	23.8±2.4	6.6±0.7	2.6±0.3
CUS, n=9	27.2±2.6	8.7±0.7	3.2±0.3
LT+ CUS, n=9	26.9±2.7	8.2±0.7	3.6±0.4
PCPA + CUS, n=9	34.2±3.1*#	9.1±0.8	3.8±0.4
DP + CUS n=9	27.6±2.6	7.8±0.8	3.1±0.3
HP+ CUS, n=9	33.8±2.9*#	8.1±0.7	4.2±0.4
LD+ CUS, n=9	29.2±2.7	8.8±0.8	2.9±0.3
MP+ CUS, n=9	28.3±2.7	9.2±0.8	4.1±0.4
7 days after CUS initiation			
Control, n=7	22.9±2.7	6.4±0.6	3.2±0.3
CUS, n=9	34.1±2.9*	9.3±0.9*	3.9±0.4
LT+ CUS, n=9	28.9±2.9	9.6±0.9*	4.1±0.4
PCPA + CUS, n=9	37.8±3.6*	12.3±1.1*	4.3±0.4*
DP + CUS n=9	31.1±2.9	9.7±0.9*	3.7±0.4
HP+ CUS, n=9	38.6±3.6*	13.4±1.3*	4.7±0.4*
LD+ CUS, n=9	29.4±2.8	10.6±0.9*	4.1±0.3
MP+ CUS, n=9	36.9±3.7*	14.6±1.2*	4.4±0.4*
14 days after CUS initiation			
Control, n=7	24.3±2.4	6.9±0.7	3.1±0.4
CUS, n=9	34.9±3.4*	12.8±1.2*	4.7±0.4*
LT+ CUS, n=9	34.3±3.1*	11.6±1.2*	4.4±0.4
PCPA + CUS, n=9	45.8±4.2*#	16.8±1.4*#	6.3±0.4*#
DP + CUS n=9	36.2±3.3*	12.8±1.3*	3.9±0.3
HP+ CUS, n=9	45.3±4.2*#	17.7±1.6*#	7.1±0.6*#
LD+ CUS, n=9	32.9±3.2*	12.4±1.2*	4.2±0.4
MP+ CUS, n=9	46.2±4.2*#	18.2±1.6*#	6.7±0.6*#
21 days after CUS initiation			
Control, n=7	22.8±2.2	7.1±0.7	2.9±0.3
CUS, n=9	38.6±3.7*	14.8±1.4*	4.9±0.5*
LT+ CUS, n=9	26.7±2.4#@	11.1±1.1#@	5.8±0.5*@
PCPA + CUS, n=9	41.9±3.8*	14.7±1.4*	7.7±0.7*#
DP + CUS n=9	25.9±2.6#@	10.2±0.9#@	5.4±0.4*
HP+ CUS, n=9	38.7±3.6*	16.2±1.6*	6.9±0.6*#
LD+ CUS, n=9	26.2±2.4#@	9.8±0.9#@	5.1±0.4*@
MP+ CUS, n=9	39.3±3.7*	14.3±1.4*	7.4±0.6*#

Notes: * – $P<0.05$ – statistical differences of the investigated parameters compared with the same in the control group; # – $P<0.05$ – statistical differences of the investigated indexes compared with the same in rats with CUS; @ – $P<0.05$ – statistical differences of the investigated indexes compared with the same in rats with CUS and modulation of corresponding neurotransmitter system activity.

The value of the studied index in rats with monoaminergic NS activity suppression on the 7th day of the trial significantly exceeded the same control index ($p<0.05$).

The number of US and CS combinations required for CAAR occurrence in rats 14 days after the trial start was 34.1±2.9, which was 43.6 % higher than the corresponding control value ($p<0.05$). The values of studied index in rats with serotonin, dopamine and noradrenergic NS activity inhibition were significantly higher when compared with such data in control and stressed rats (in all cases $p<0.05$). The studied value in rats of the rest experimental groups was comparable to similar index in rats with CUS ($p<0.05$ vs control values).

On the 21st day of the trial the studied learning index in rats with serotonin, dopamine and noradrenergic NS activation was comparable to corresponding control data ($p>0.05$) and was also significantly less pertaining the similar indexes in stressed rats and in CUS rats with corresponding NS activity inhibition (in all cases $p<0.05$). The value of the studied index in rats with monoaminergic NS activity inhibition at this time of the trial significantly exceeded the corresponding control index ($p<0.05$).

On the 7th and the 14th days of the trial, the number of US and CS combinations required to CAAR reproduction in stressed rats 1 day after reflex development with monoaminergic NS activity modulation significantly (in the range from 45.3 % to 267.8 %) exceeded the corresponding control indexes (in all cases ($p<0.05$). On the 14th day of the trial the studied indexes in rats with serotonin, dopamine, and noradrenergic NS activity inhibition exceeded the corresponding indexes in rats with CUS (in the range from 31.3 % to 42.2 %; $p<0.05$).

On the 21st day of the trial, the number of US and CS combinations required to CAAR reproduction 1 day after its development in stressed rats with the studied monoaminergic NS activation was less comparing with the similar index in rats with CUS and the same index in stressed rats with corresponding NS inhibition (in all cases $p<0.05$).

During the first 14 days of the trial, the number of US and CS combinations required to CAAR reproduction 7 days after its production was comparable in stressed and intact rats ($p>0.05$). At the same time, on the 7th day of the trial, the value of the studied index in rats with serotonin, dopamine and noradrenergic NS activity inhibition was significantly higher pertaining the corresponding control values ($p<<0.05$).

Starting from the 14th day of the trial, the value of the studied index was significantly higher than the control and the indexes in rats with CUS (in all cases $p<0.05$). The value of the studied indexes in rats with CUS and serotonin, dopamine and noradrenergic NS activity suppression exceeded similar control values and those obtained in stressed rats (in all cases $p<0.05$).

Similar dynamics of the studied parameter changes was also registered on the 21st day of the trial ($p<0.05$). At this time, the values of the studied parameter in rats with serotonin, dopamine, and adrenergic NS activation had significant statistical differences vs the corresponding indexes in rats with CUS and such indexes in stressed rats with corresponding NS activity suppression (in all cases $p<0.05$).

The relative values of the integral index of "preservation" which allows to assess the effect of certain influences on the skill (engrams) retention are presented below (Fig. 1). The value of "preservation" in CUS dynamics gradually decreases, reaching minimal values starting from the 14th day of the trial ($p<0.05$). On the 1st day of the trial, the value of the studied index in stressed rats with previously inhibited the serotoninergic and dopaminergic NS activity turned out to be significantly higher when compared with similar data in rats with CUS ($p<0.05$). However, this index was twisted throughout the CUS modelling and did not reveal any advantage in case of the studied monoaminergic NS activity modulation ($p>0.05$).

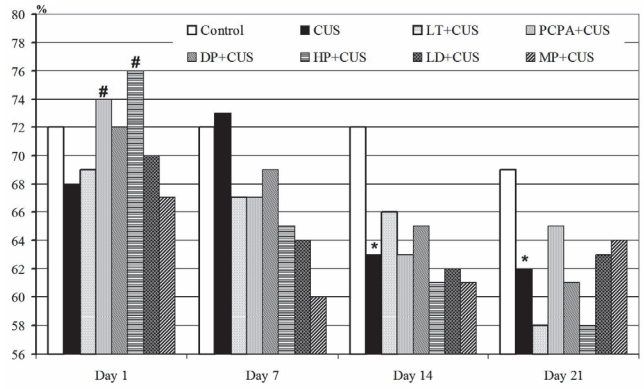

Fig. 1. The impact of monoaminergic NS activity modulation on the "preservation" index in rats in conditions of chronic unpredictable stress. Notes: * – $P<0.05$ – statistical differences of the investigated parameters compared with the same in the control group; # – $P<0.05$ – statistical differences of the investigated indexes compared with the same in rats with CUS.

Thus, the data obtained indicate the mnestic disorders formation in rats in dynamics of CUS formation which were expressed of learning processes failure and in short- and long-term memory expression fail. The studied indexes of cognitive disorders were formed from the 1st day of the trial, progressed in its dynamics, were maximally expressed starting from the 14th day and lasted for 3 weeks of experiment.

The materials obtained analysis indicates the monoaminergic neurotransmitter system important pathogenetic role in mnestic disorders formation in chronic stress. Precisely, both the serotonin and dopaminergic NS activity inhibition in a greater extent and adrenergic NS to a lesser extent, starting from the 7th day of the trial, significantly worsened the ability of stressed rats to learn and to demonstrate the short-and long-term memory. It should be noted that serotonin, dopamine and adrenergic NS activation in the postponed period of the trial contributed to compromised cognitive

functions normalization. The impact of monoaminergic neurotransmission modulation on mnestic disorders expression became marked starting from the 14th day of the trial and lasted until its end. That is we are talking about a long-term mediation of learning and memory processes by serotonin, dopamine and adrenergic NS in chronic stress conditions.

It should be noted that monoaminergic neurotransmission modulation in the dynamics of the entire experiment did not affect the relative rate of memory engram formation and storage – the "preservation" index.

With the data obtained discussion purpose we will pay attention to the following two fundamental aspects.

Firstly, we see a fundamental novelty in the methodological support of these studies not only in a qualitatively new model of chronic stress, which is unpredictable, but also in the fact that the pathophysiological mechanisms of stress-induced disorders of the body functional systems activity are not yet fully studied from the point of view of their integral communication. It should not be forgotten that body's functional reserve and the regulatory systems adaptation change in such conditions that can induce the general maladaptation development and pathological disintegration of organs and systems with subsequent perfusion and microcirculatory blood supply disorders and at least ischemia [2].

Secondly, it is interesting to explain the detailed mechanism of stress-induced mnestic effects from the point of view of monoaminergic NS activity modulation taking into account the subcortical regulation of sleep-wakefulness cycle, the emotional sphere, attention, learning, formation and preservation of memory engrams, concentration of attention, etc., which significantly affects the mnestic processes stability. Here we stress that individual neurons and large-scale neuronal groups that secrete and interfere with each other using serotonin, dopamine, adrenaline and noradrenaline, as well as GABA, from one side, are extremely sensitive to neurotropic damaging, including stressogenic influences, episodes of ischemia, etc., which sequences are spoiled neurotransmitters release by subcortical structures and brainstem, long-term disorders of synaptogenesis and axonal growth along with synaptic communication mechanism inhibition. All of the above are the leading chains of pathophysiological mechanisms initiated by altering stressogenic factors influence which have an obvious negative impact on the course of mnestic processes [9, 11].

Discussing the data obtained we note that our results are consistent in some way with proved monoaminergic NS involvement in motor functions, muscle activity, neurological deficits and emotional behavior mediating in chronic stress [1] as well as in conditions of traumatic brain injury [2, 14] which, we believe, has a fundamental explanation, given the localization and secretory activity of the leading nuclear groups in the brain that release serotonin, dopamine and adrenaline, as well as taking into account their functional load [9].

Muscle activity mediation by serotonin and dopaminergic NS was confirmed in clinical observations which is used by clinicians in body's physical activity restoring [6].

We consider important to explain the methodological background of our research. Learning processes via CAAR modelling were studied in dynamics of CUS induction, as well as the ability to preserve the formed reflex during 7 days which corresponds to time intervals of short- and long-term memory. We succeeded to trace the process of memory engram formation and the ability to preserve (or lose) it in the model conditions. The duration of information pattern preservation in the short-term memory determined by a pool of neurotransmitter (neurotransmitters) time in the synaptic cleft after the stimulus [11]. There is evidence that such informative "marking" occurs not by one neurotransmitter but by the synchronized influx of several neurotransmitters to relevant neuronal formations of the brain [5].

Discussing the biochemical significance of the results obtained we emphasize the proved adrenergic NS deprivation as a leading mechanism of memory impairment in the elderly [4]. It was proved that in old animals that phasicity of GABA and serotonin release and their clearance are impaired in the same way as it occurs with adrenergic mediation [4, 12]. The impact of dopaminergic NA on cognitive processes is confirmed by the leading importance of its nigrostriatal, mesocortical and mesolimbic components in the aspect of working memory size maintenance and regulation [5, 11].

Our data are somewhat consistent with the above statements since monoaminergic NS activity inhibition worsened the expression of mnestic functions in CUS dynamics and vice versa.

Resuming, we emphasize the importance of taking into account the monoaminergic neurotransmission functional activity when analyzing the organism's cognitive capabilities in each specific case. With the aim of prolonged single (or combined) stressful impact pathogenetically oriented pharmacocorrection it is desirable to achieve serotonin, dopamine and noradrenergic neurotransmission activation that will allow to switch in sanogenetic mechanisms.

In our opinion, this is a promising possibility of brain excitability regulation by monoaminergic NS activity modulation that we consider a necessary and sufficient component of sanogenic mechanisms activation in conditions of chronic stressor influences characterized by damaging neurotropic impact. In this case, endogenous activation of protective mechanisms is achieved which initiates complex cascade physiological and biochemical sanogenic processes.

We are confident that data obtained are experimental evidence monoaminergic neurotransmission activation clinical effects testing reasonability in chronic stress conditions while performing and determining the clinical efficacy of treatment regimens for mnestic disorders complex pathogenetic therapy in patients with chronic unpredictable stress manifestations.

Conclusions

1. The expressed mnestic disorders are developed in rats during the CUS modelling manifested by deterioration of learning, formation and preservation of memory engrams.

2. Mnestic disorders are developed from the 1st day of CUS induction, progress in its dynamics and are maximally expressed from the 14th day of the trial.

3. Serotonin, dopamine and adrenergic NS activity suppression starting from the 7th day of the trial significantly impaired rats learning and short- and long-term memory.

4. Serotonin, dopamine and adrenergic NS activity increase from the 21st day of the trial contributed to impaired mnestic functions normalization.

5. It is important to take into account the monoaminergic neurotransmission functional activity while analyzing the persons cognitive capabilities in chronic stress conditions. It is desirable to achieve serotonin, dopamine and noradrenergic neurotransmission activation that will allow to switch in sanogenetic mechanisms.

6. The data obtained are experimental evidence of monoaminergic neurotransmission activation clinical effects testing reasonability in chronic stress conditions while performing and determining the clinical efficacy of treatment regimens for mnestic disorders complex pathogenetic therapy in patients with chronic unpredictable stress manifestations.

Prospects for further research are aimed at further experimental verification of the validity of the used model of chronic unpredictable stress to such a clinical condition and mandatory verification in these conditions of the restoration of other body functions under chronic stress due to the activation of sanogenetic mechanisms by modulating monoaminergic neurotransmission. An additional direction of research is considered to be the experimental substantiation of the expediency of minimizing manifestations and eliminating amnestic effects by modulating a certain monoaminergic neurotransmission.

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