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THE EFFECT OF ACUTE MENTAL STRESS ON THE EXCHANGE OF MONOAMINES IN THE MESOCORTICAL AND NIGROSTRIATAL SYSTEMS OF THE RAT BRAIN

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Background. Mesocortical and nigrostriatal dopaminergic systems are highly sensitive to stressful events. One of the most adequate models of acute psychogenic stress in animals is the death of a partner upon presentation of a predator.
Aim. To study the content of dopamine (DA), serotonin and their metabolites: dioxyphenylacetic (DOPAC), homovanillic and 5-hydroxyindoleacetic (5-HIAA) acids in the prefrontal cortex, striatum, and ventral tegmental area in rats on days 3, 7, and 14 after the acute psychogenic stress of the death of a partner upon presentation of a predator.
Materials and methods. 28 male Wistar rats were studied. Acute single psychotraumatic situation was used. A group of rats was placed in a tiger python terrarium. One animal died as a result of its nutritional needs, the rest of the rats experienced the death of a partner. The content of monoamines in the brain structures was carried out by high performance liquid chromatography with electrochemical detection.
Results. Changes in the content of monoamines in the prefrontal cortex, striatum, and ventral tegmental area were found on the 7 and 14 days after the presentation of the predator. In the ventral tegmental area on the 7 day, there was an increase in the DOPAC/DA ratio and an increase in the serotonin metabolite 5-HIAA, which reflects an increase in the activity of dopamine and serotonin. In the prefrontal cortex on the 14 day, the DOPAC content and the DOPAC/DA index decreased. The 5-HIAA content in the prefrontal cortex and the 5-HIAA/5-HT value also significantly decreased.
Conclusions. Changes in the metabolism of monoamines after presentation of a predator develop gradually: increase of the dopamine and serotonin activity in the ventral tegmental area was noted on the 7 day after presentation of the predator, decrease in their activity in the striatum and prefrontal cortex only on the 14 day, reflecting the development of depressive states and post-traumatic stress disorder.

Keywords: psychogenic stress; predator; dopamine; serotonin; mesocortical system; striatum.

ДЕЙСТВИЕ ОСТРОГО ПСИХИЧЕСКОГО СТРЕССА НА ОБМЕН МОНОАМИНОВ В МЕЗОКОРТИКАЛЬНОЙ И НИГРОСТРИАТНОЙ СИСТЕМАХ ГОЛОВНОГО МОЗГА КРЫС

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Актуальность. Мезокортикальная и нигростриатная дофаминергические системы высокочувствительны к стрессорным психогенным воздействиям. Одна из наиболее адекватных моделей острого психогенного стресса у животных — это ситуация гибели партнера при предъявлении хищника.
Цель исследования — изучить динамику уровня дофамина (ДА), серотонина и их метаболитов: диоксифенилуксусной (ДОФУК), гомованилиновой и 5-гидроксииндолуксусной (5-ГИУК) кислот — в префронтальной коре, стриатуме и вентральной области покрышки у крыс на 3, 7 и 14-й дни после острого психогенного воздействия ситуации гибели партнера при предъявлении хищника.
Материалы и методы. В работе было использовано 28 крыс-самцов линии Вистар. Применяли острую однократную психотравмирующую ситуацию. Крыс помещали в террариум к тигровому питону. Одно животное погибало в результате пищевых потребностей питона, остальные крысы переживали ситуацию гибели партнера.

Определение уровня моноаминов в структурах мозга проводили методом высокоэффективной жидкостной хроматографии с электрохимической детекцией.

Результаты. Обнаружены изменения уровня моноаминов и их метаболитов в префронтальной коре, стриатуме и вентральной области покрышки на 7-й и 14-й дни после предъявления хищника. В вентральной области покрышки на 7-й день отмечалось повышение индекса ДОФУК/ДА и уровня метаболита серотонина 5-ГИУК, что отражает возрастание активности дофамин- и серотонинергической систем. В префронтальной коре на 14-й день содержание ДОФУК и показатель ДОФУК/ДА снижались. Уровень 5-ГИУК и индекс 5-ГИУК/5-ГТ в префронтальной коре так же значительно снижались.

Заключение. Изменения обмена моноаминов развиваются постепенно после предъявления хищника, в вентральной области покрышки отмечается повышение активности дофаминовой и серотониновой систем на 7-й день после предъявления хищника, а на 14-й день снижение их активности в стриатуме и префронтальной коре, отражая развитие депрессивноподобных состояний и посттравматического стрессорного расстройства.

Ключевые слова: психогенный стресс; хищник; дофамин; серотонин; мезокортикальная система; стриатум.

BACKGROUND

The study of the consequences of the influence of extreme environmental factors on the body is of great medical and biological importance [4]. Stress factors cause mobilization of body systems, which is accompanied by the release of adrenaline, norepinephrine, and corticosteroids from the adrenal glands. The stress response under the influence of environmental factors (stressors) can cause both protective and damaging effects, which are manifested by a shift in various systems and indicators, including the metabolism of brain monoamines [11]. The reactivity to the action of stressors is associated with the activities of the dopaminergic, noradrenergic, and serotonergic systems of the brain [2]. The brain structures that are highly sensitive to stress factors include the mesocortical dopaminergic system, prefrontal cortex, ventral tegmental area, and striatum, which belong to the nigrostriatal dopaminergic system [13]. One of the most adequate models of acute psychogenic effects on animals is the situation of the death of a partner upon the presentation of a predator [3]. Despite publications on the analysis of the effects of acute mental stress on the functioning of the neurochemical systems in the central nervous system, there is a clear lack of research on the dynamics of changes in the levels and metabolism of monoamines in stress-reactive dopaminergic structures of the brain. Thus, a comparative study of the time evolution of the effects of acute mental stress on the levels and metabolism of monoamines in the structures of the mesocortical and nigrostriatal dopaminergic systems of the brain is desirable.

The study aimed to perform a comparative analysis of the levels of dopamine (DA), serotonin (5-HT), and their metabolites in the prefrontal cortex, striatum, and ventral tegmental area in rats on days 3, 7, and 14 after the acute psychogenic effect of the death of a partner upon the presentation of a predator.

MATERIALS AND METHODS

The study used 28 male Wistar rats obtained from the nursery of laboratory animals Rappolovo (Leningrad region). The animals were kept under vivarium conditions in four standard cages in groups of seven with free access to water and food under artificial 12-h illumination from 8.00 to 20.00 at a temperature of 22 ± 2°C. All experiments were conducted in accordance with the Geneva Convention "International Guiding Principles for Biomedical Research Involving Animals" (Geneva, 1990), Declaration of Helsinki 2000, and GLP protocol on the humane treatment of animals (Directive of the European Community No. 2010/63/EC), with the approval of the ethics committee of the Institute of Experimental Medicine. The experiment was started no earlier than 3 weeks after the arrival of rats from the nursery.

The rats kept in cage 1 were not exposed to stress and were used as controls ($n = 7$). Animals kept in three cages ($n = 21$) were subjected to an acute single psychotraumatic situation. To do this, all rats were simultaneously placed in a terrarium (1.2 × 0.7 × 1 m) with a black-tailed python. After one animal died as a result of satisfying its nutritional needs, the remaining rats were taken from the terrarium and randomly assigned to three living cages [3]. On days 3 ($n = 6$), 7 ($n = 7$), and 14 ($n = 7$) after the presentation of the predator, the rats were decapitated. Euthanasia of control animals was performed similarly. From the coronal sections of the brain, the prefrontal cortex, striatum, and ventral tegmental area were isolated on ice. Rat brain samples were frozen and stored until chromatographic analysis at –80°C. Brain samples were homogenized in 0.1 N HCl solution and centrifuged at 14,000 g for 15 min. The levels of DA, dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-HT, and hydroxyindoleacetic acid (5-HIAA) were determined by high-performance liquid chromatography with electrochemical detection

using a Beckman Coulter chromatographic system with an amperometric detector LC4C (BAS). A Phenomenex analytical column (4.6 × 250.0 mm) with a SphereClone ODS(2) sorbent was loaded with 20 μL of the brain sample supernatant. The level of monoamines and their metabolites was measured at a potential of +0.70 V. The mobile phase contained 5.5 mM citrate-phosphate buffer, 0.7 mM octanesulfonic acid, 0.5 mM EDTA, and 8% acetonitrile (pH 3.0). The flow rate of the mobile phase was 1 mL/min. The level of monoamines and their metabolites in brain structures was expressed in ng/mg of tissue.

Data obtained were analyzed using the GraphPad PRISM 6.0 statistical software package. Differences in the rates of monoamine metabolism in brain structures were assessed using one-way analysis of variance using the Bonferroni correction for multiple comparisons. Differences were considered significant at $p < 0.05$. Data are presented as the arithmetic mean ± standard error of the arithmetic mean.

RESULTS AND DISCUSSION

In this study, we analyzed the levels of DA, 5-HT, and their metabolites (DOPAC, HVA, and 5-HIAA) in brain structures on days 3, 7, and 14 after predator presentation, by high-performance liquid chromatography with electrochemical detection. In rats, significant changes were registered in the prefrontal cortex only on day 14 after the presentation of a predator compared with control (intact) animals (Figs. 1 and 2). No significant differences were noted in the first 2 weeks after the presentation of a predator. The level of DOPAC on day 14 after the predator presentation decreased

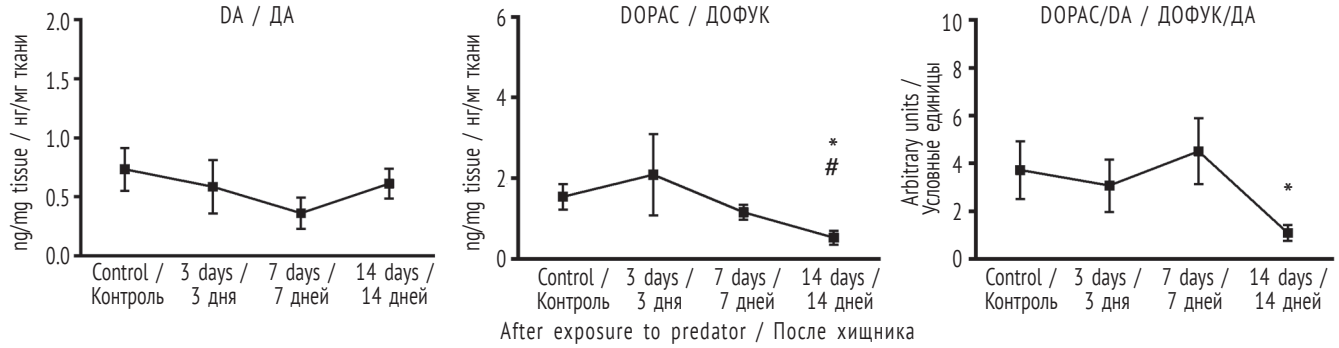

Fig. 1. Content of dopamine (DA) and its metabolite DOPAC in the prefrontal cortex rats on 3, 7 and 14 days after exposure to predator. *$p < 0.05$ – significantly different from control group; #$p < 0.05$ – parameter is significantly different between rats on 7 and 14 days after stress

Рис. 1. Содержание дофамина (ДА) и его метаболита — диоксифенилуксусной кислоты (ДОФУК) в префронтальной коре мозга крыс на 3, 7 и 14-й дни после предъявления хищника. *$p < 0,05$ — достоверные отличия по сравнению с контрольной группой; #$p < 0,05$ — показатель достоверно отличается между группами крыс 7-го и 14-го дня после стрессорного воздействия

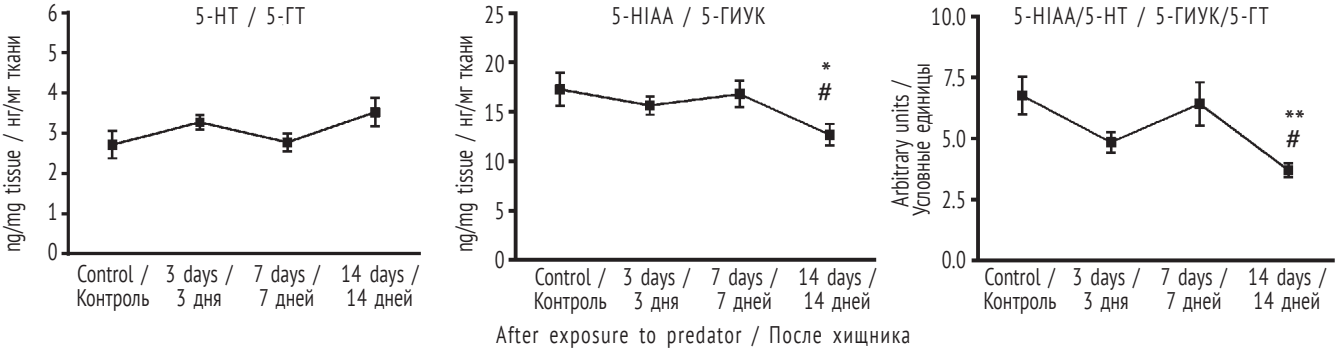

Fig. 2. Content of serotonin (5-HT) and its metabolite 5-HIAA in the prefrontal cortex rats on 3, 7 and 14 days after exposure to predator. *$p < 0.05$, **$p < 0.01$ – significantly different from control group; #$p < 0.05$ – parameter is significantly different between rats on 7 and 14 days after stress

Рис. 2. Содержание серотонина (5-ГТ) и его метаболита — гидроксииндолуксусной кислоты (5-ГИУК) в префронтальной коре мозга крыс на 3-й, 7-й и 14-й дни после предъявления хищника. *$p < 0,05$, **$p < 0,01$ — достоверные отличия по сравнению с контрольной группой; #$p < 0,05$ — показатель достоверно отличается между группами крыс 7-го и 14-го дня после стрессорного воздействия

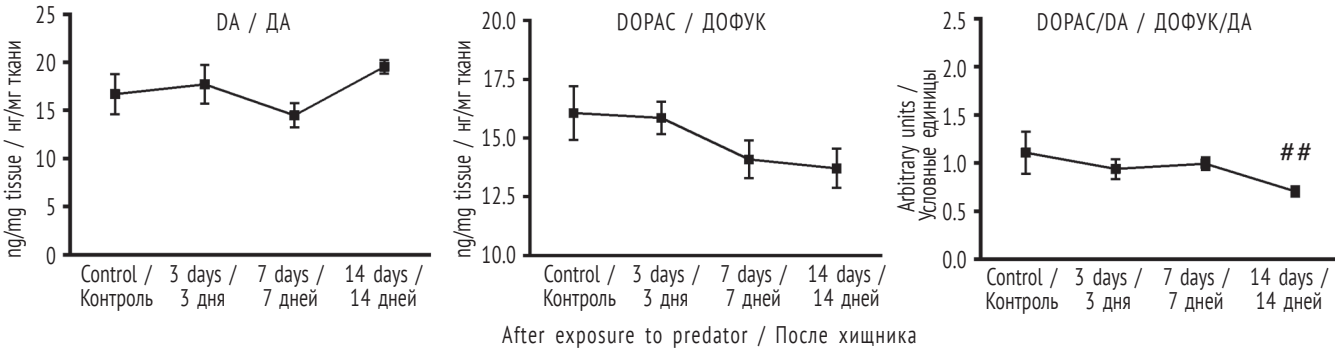

Fig. 3. Content of dopamine and its metabolite DOPAC in the striatum rats on 3, 7 and 14 days after exposure to predator. ##$p < 0.01$ – parameter is significantly different between rats on 7 and 14 days after stress

Рис. 3. Содержание дофамина (ДА) и его метаболита — диоксифенилуксусной кислоты (ДОФУК) в стриатуме головного мозга крыс на 3-й, 7-й и 14-й дни после предъявления хищника. ##$p < 0,01$ — показатель достоверно отличается между группами крыс 7-го и 14-го дня после стрессорного воздействия

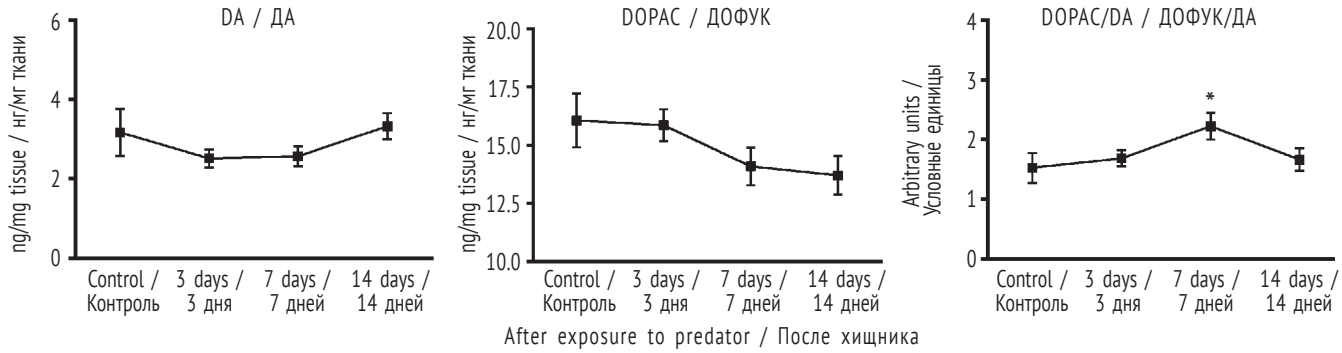

Fig. 4. Content of dopamine (DA) and its metabolite DOPAC in the ventral tegmental area rats on 3, 7 and 14 days after exposure to predator. *$p < 0.05$ – significantly different from control group

Рис. 4. Содержание дофамина (ДА) и его метаболита — диоксифенилуксусной кислоты (ДОФУК) в вентральной области покрышки среднего мозга крыс на 3, 7 и 14-й дни после предъявления хищника. *$p < 0,05$ — отличия от показателя, измеренного у интактных крыс

from 1.54 ± 0.31 to 0.52 ± 0.18 ng/mg of tissue ($p < 0.05$) compared with the values measured in control rats. Moreover, the level of DOPAC in the prefrontal cortex on day 14 after the predator presentation was significantly lower than the values measured 7 days after the stress exposure ($p < 0.05$). The DOPAC/DA index also decreased only on day 14 after the predator was presented compared with the control animals, namely, from 3.73 ± 1.21 to 1.10 ± 0.33 ($p < 0.05$) (Fig. 1). The 5-HIAA level decreased from 17.29 ± 1.68 to 12.70 ± 1.08 ng/mg of tissue ($p < 0.05$) compared with the values measured in control rats. Furthermore, the 5-HIAA level in the prefrontal cortex on day 14 after the predator presentation was significantly lower than the values measured on day 7 after the stress exposure ($p < 0.05$). Compared with the index in control animals, the 5-HIAA/5-HT index also decreased on day 14 after the predator was presented, from 6.75 ± 0.77 to 3.70 ± 0.28 ($p < 0.01$) (Fig. 2). Moreover, the 5-HIAA/5-HT ratio in the prefrontal cortex on day 14 after the predator presentation was significantly lower than the values measured 7 days after the stress exposure ($p < 0.05$).

Compared with the control animals, significant changes in the rat striatum were registered only on day 14 after the presentation of the predator. In the first 2 weeks after predator presentation, no significant differences were noted. The DOPAC/DA ratio decreased from 1.11 ± 0.22 to 0.71 ± 0.05 ($p < 0.01$) compared with values measured 7 days after stress exposure (Fig. 3).

In the ventral tegmental area, significant changes were registered on day 7 after the predator presentation in comparison with the control animals (Fig. 4, 5). In week 1 after the predator presentation, no significant differences were noted, just as no differences were registered on day 14 after the stress exposure. The DOPAC/DA ratio increased from 1.52 ± 0.25 to 2.22 ± 0.22 ($p < 0.05$) on day 7 after the predator presentation, compared with the values measured in control rats (Fig. 4).

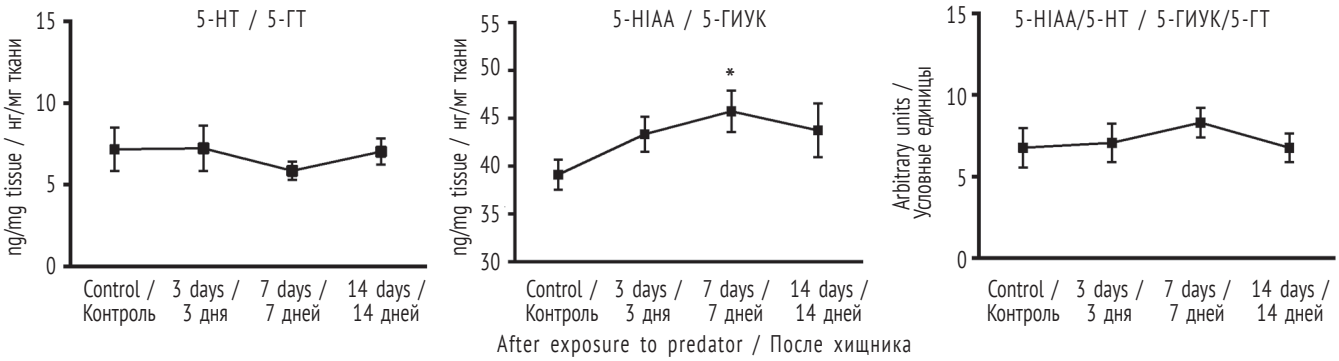

Fig. 5. Content of serotonin and its metabolite 5-HIAA in the ventral tegmental area rats on 3, 7 and 14 days after exposure to predator. *$p < 0.05$ – significantly different from control group

Рис. 5. Содержание серотонина (5-ГТ) и его метаболита — гидроксииндолуксусной кислоты (5-ГИУК) в вентральной области покрышки среднего мозга крыс на 3-й, 7-й и 14-й дни после предъявления хищника. *$p < 0,05$ — отличия от показателя, измеренного у интактных крыс

The 5-HIAA level on day 7 after the predator presentation increased from 39.1 ± 1.6 to 45.7 ± 2.2 ng/mg of tissue ($p < 0.05$) compared with the values measured in control rats (Fig. 5).

The HVA levels in the studied brain structures in control and experimental animals on days 3, 7, and 14 after acute stress were not different. No significant differences were found in the HVA/DA ratio.

Thus, this study shows changes in the levels of monoamines and their metabolites in the mesocortical (ventral tegmental area, and prefrontal cortex) and nigrostriatal (striatum) dopaminergic systems of the brain only on days 7 and 14 after the predator presentation. This proves that these changes after acute stress develop gradually. Post-stress changes were registered in the ventral tegmental area on day 7 and in the striatum and prefrontal cortex on day 14 after the stress exposure. Thus, stress affects earlier the state of monoaminergic systems in the brainstem, where the bodies of the corresponding neurons are localized. The increase in DOPAC/DA ratio and an increase in the level of the 5-HT metabolite 5-HIAA in the ventral tegmental area reflect an increase in the activity of the dopaminergic and serotonergic systems. By contrast, in stressed rats, DA metabolism in the prefrontal cortex and striatum decreased. In addition, indicators of 5-HT metabolism (5-HIAA level and 5-HIAA/5-HT ratio) also significantly decreased in the prefrontal cortex. Thus, changes in the activity of monoaminergic systems in the brainstem and forebrain structures were opposite, as it increased in the ventral tegmental area, whereas it decreased in the striatum and prefrontal cortex.

The reactions of the dopaminergic system of the brain are of interest, first, because it participates in the genesis of human psychopathological states, which are known to be aggravated after stress. Mesocortical and mesolimbic DA pathways from the ventral tegmental area to the telencephalon are involved in the mechanisms of memory and emotion. Dopaminergic cells of the substantia nigra are also projected into the striatum and form the nigrostriatal system, which is involved in the organization of motor reactions. A study reported that the mesocortical dopaminergic system is more sensitive to stress than the nigrostriatal system [5]. The results of our experiments ascertain these data, showing that the peak of delayed stress-induced changes occurs in an earlier period of the experiment (7 days) in the midbrain region than in the structures of the forebrain (14 days). Under conditions of space-restriction stress, an initial increase in mesolimbic DA release was followed by its decrease, suggesting that repeated exposure to the same stressor leads to the inhibition rather than the activation of dopaminergic neurons [9]. Mice with knockout of the DA transporter (DAT) gene, which had high levels of extracellular DA, were highly reactive in response to novelty stress compared with control animals [15]. Since DOPAC is formed under the influence of monoamine oxidase, an enzyme localized intracellularly, the level of this metabolite may indicate the intensity of DA reuptake. Therefore, the post-stress changes in DA metabolism revealed are possibly associated with changes in DAT activity. Social damage in the alien-resident test in male rats leads to a decrease in DAT in the striatum [9], which is consistent with our results on a decrease in the DOPAC/DA ratio on day 14 after stress exposure. In the literature, stress changes not only DA metabolism but also the state of receptors for this mediator. In the model of psychosocial stress in shrews, the count of D1 receptors in the striatum and prefrontal

cortex increased [12]. The above changes in DAT and DA receptors indicate a stress-induced disorder in DA release. A decrease in DA release, may also cause anhedonia and a decrease in motivation in depression [14]. The data obtained in this study are also largely consistent with the data on the level and metabolism of monoamines after acute mental stress, particularly electrocutaneous stimulation in rats. In stressed rats, DA resynthesis was ahead of its release [1]. Possibly, this may have provided the delayed effects noted in the present work on day 14 after the stress exposure in the structures of the nigrostriatal and mesocortical systems of the rat brain.

Changes in serotonergic neurons are known to underlie depressive disorders. The most widely used antidepressants serve as 5-HT reuptake inhibitors and increase its extracellular level [6]. The action of these drugs are noted only after 7–14 days, in accordance with the delayed changes in the metabolism of 5-HT in our studies. 5-HT is known to regulate mood, and its receptors become targets for several psychotropic drugs [6]. Rhesus monkeys with a short sequence of the 5-HT reuptake transporter allele have a low concentration of 5-HIAA in the cerebrospinal fluid. This is consistent with the statement that low 5-HT levels in the brain, corresponding to a decrease in the activity of the serotonergic system, impair emotionality. Moreover, people with a high level of expression of the 5-HT breakdown enzyme monoamine oxidase-A (MAO-A) are less likely to develop post-traumatic stress disorders [7]. According to the literature, stress exposure increases the concentration of 5-HT and its metabolites in some brain regions. In addition, stress causes changes in brain areas that serve as targets for serotonergic neurons. Space-restriction stress caused an increase in 5-HT metabolism and reduced the activity of 5-HT1A receptors in rat hippocampus, which the present authors explain by a stress-dependent increase in the level of glucocorticoids that regulate the transcription of many genes [8]. Repeated forced swimming caused an increase in 5-HT levels in the rat striatum [10]. However, according to our data, the delayed effects of stress on the serotonergic system in the striatum include a change in the concentration of not the mediator itself but its metabolite, 5-HIAA, which may be associated with an increase in 5-HT transporter activity. This assumption requires direct experimental verification.

CONCLUSION

In this study, changes in the levels of monoamines and their metabolites in the prefrontal cortex, striatum, and ventral region of the tegmental area were registered on days 7 and 14 after the predator presentation. On day 3 after stress exposure, no significant changes in the parameters of the metabolism of the studied mediators were found. This proves that changes in the state of monoaminergic systems after the presentation of a predator develop gradually, reflecting the delayed development of a depressive-like state.

In the ventral tegmental area, an increase in DA activity and 5-HT systems was observed on day 7 after the stress exposure. Opposite and later changes were noted in the striatum and prefrontal cortex, namely, a decrease in the activity of the DA and 5-HT systems on day 14 after the predator presentation. The effect of acute predator presentation stress on the state of monoaminergic systems is possibly associated with the course of an initial adaptive reaction, characterized by the activation of brainstem structures, and subsequent disadaptation, namely, a decrease in the activity of telencephalon structures, revealing the development of post-traumatic stress disorder.

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