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EXPERIMENTAL ARTICLES

The Dynamics of Monoamine Metabolism in Rat Brain Structures in the Late Period after Exposure to Accelerated Carbon Ions

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Abstract—We studied the effect of carbon ions (^{12}C) with an energy of 500 MeV/nucleon at a dose of 1 Gy on monoamine metabolism in the brains of rats of different ages. Neurochemical parameters that characterize the distribution of noradrenaline (NA), dopamine (DA), serotonin (5-HT), and its metabolites were evaluated during 2 months on days 30 and 90 after the exposure to radiation. We studied the prefrontal cortex, hypothalamus, hippocampus, and striatum. The results showed changes in the activities of the NA, DA, and 5-HT systems in rats of different age groups after exposure to radiation. The most prominent differences in the exposed and control animals were observed in the prefrontal cortex and hypothalamus, which indicates the important role of these brain regions in long-term effects of exposure to radiation on the central nervous system. A comparison of animals from different age groups showed a decrease in the intensity of the temporal changes in all analyzed structures except the striatum in the exposed rats. Based on these findings, we assumed that the activation of compensatory and repairing mechanisms occurs in the late post-radiation period. At relatively low linear energy transfer of particles (10.6 keV/μm), it may lead to the partial recovery of brain functions that were impaired by radiation. At higher values of the linear energy transfer, the compensatory and recovery processes are activated to a lesser degree and functional impairment increases with time.

Keywords: late effects, monoamines, metabolites, heavy ions, the central nervous system

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INTRODUCTION

Recent experimental data show the high radiosensitivity of certain parts of the brain to heavy charged particles of high energy [1–3]. However, many aspects of various neuroradiobiological effects of ionizing radiation with different physical characteristics remain unclear. The importance of the study of the mechanisms that underlie the currently known effects is determined by a wide range of scientific and practical problems. They include problems of the treatment of neoplastic diseases and other pathologies of the brain using charged particle beams. These studies are of particular importance due to their connection with problems of space radiobiology. First of all, these are related to the assessment of the risks of the possible negative influence of heavy charged particles of galactic cosmic rays (GCRs) on the functional state of the central nervous system of astronauts during deep space flights [1, 2]. These flights have a high risk of exposure of the crew to heavy ions with high energy, whose range is very broad and reaches ultrahigh levels of 10^{20} eV [4, 5]. Maintenance of the radiation safety of astronauts by physical means of protection will not be possible in the near future. The energy transfer from heavy charged particles to biological structures determines the type and specificity of various effects of GCR exposure. The current data on the effects of heavy charged particles on the central nervous system at doses that may be actually received by astronauts during an interplanetary flight demonstrate a number of structural and functional disorders that underlie changes in the behavior and memory of experimental animals after exposure. The presently known disorders were reviewed in [1–3, 6, 7].

The studies of late changes in the central nervous system associated with neurochemical abnormalities in the brain after exposure are of particular interest. A number of recent studies have been focused on the levels of monoamines and their metabolites in various brain structures that are actively involved in behavior and motor control that form the emotional and motivational state [8–10]. These studies were conducted in

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rats; high-energy protons and accelerated heavy ions were used as a damaging factor [6, 7]. However, these experiments mainly concerned only short periods after an exposure that did not exceed 7 days. In this context, the aim of this work was to study late changes in monoamine metabolism that were observed in the 2-month period after exposure to carbon ions (^{12}C).

MATERIALS AND METHODS

Animals. The study was performed with 20 male Sprague-Dawley rats at ages of 7–8 weeks. The body weight of the rats was 190–210 g. The animals were purchased from the Puschino laboratory animal nursery and were pre-adapted to the conditions of the vivarium for 7 days. Five animals per cage were kept under natural lighting conditions with daylight duration of approximately 8 hours with free access to food and water. The average age of the animals at the time of exposure was 2 months. After 30 and 90 days after the exposure, five control and five exposed rats at each time period were decapitated. Animals were tested at the age of 3 and 5 months on average; the time interval between the two experiments was 2 months. All animal procedures were performed in accordance with the Regulations that were approved by the bioethical committees of the Institute of Biomedical Problems and the Institute of Higher Nervous Activity and Neurophysiology.

Exposure procedure. The animals were divided into two equal groups of ten animals. The rat groups were subjected to single total irradiation with accelerated ions of ^{12}C at a dose of 1 Gy. The particle energy was 500 MeV/nucleon, the linear energy transfer (LET) was 10.6 keV/μm, and the dose rate was 0.03 Gy/min. Exposure to radiation was performed by a Nuclotron beam accelerator at the Joint Institute for Nuclear Research (Dubna). Rats of the second (control) group were sham-exposed by keeping the animals under similar conditions excluding the effects of radiation. The absorbed dose was measured in an air ionization chamber with a 4.2×4.2 cm^2 sensitive area. A quasi-homogeneous radiation field was created by defocusing the beam of ions with magnetic lenses in front of the exposed spot. The inhomogeneity of the field on the X and Y coordinates did not exceed ± 5% within the irradiated region. The ionization chamber was calibrated to measure the particle flux using activation detectors or scintillation counters. The total error of the absorbed dose evaluation did not exceed 10%.

Neurochemical studies. After decapitation of animals, four structures were extracted from the brain: the prefrontal cortex, hypothalamus, hippocampus, and striatum. Structures were removed on ice, weighed, and frozen in liquid nitrogen. Samples were stored in a refrigerator at –80°C.

For the analysis, tissue samples were homogenized in a glass homogenizer with a teflon pestle (0.2 mm) at 4°C and 3000 revolutions per min. The 0.1 N $HClO_4$ solution with the addition of an internal standard DOBA (3,4-dioxy-benzylamine), which is a catecholamine that is absent in the native tissue, at concentrations of 0.5 nmol/mL was used as the homogenization and isolating medium. The brain structures were homogenized in a 20-fold volume of isolation medium. Centrifugation of samples was conducted for 15 minutes at 4°C and 10000 *g*. The supernatant was used to determine the concentration of monoamines and their metabolites. All analytical procedures were conducted in accordance with the method requirements for high pressure liquid chromatography with electrochemical detection (HPLC-ED). For the analysis of the samples, a LC304T chromatograph (BAS, West Lafayette, United States) with a Rheodyne 7125 injector, and a loop for applying 20 μL samples were used [6]. The analyzed substances were separated on a reversed-phase column ReproSil Pur, ODS 3, 4 × 100 mm, 3 μm (Dr. Majsch GMBH, Elsiko, Russia). A PM80 pump (BAS, United States) with an elution rate of the mobile phase of 1.0 mL/min at a pressure of 200 atm was used. The mobile phase was 0.1 M citrate-phosphate buffer containing 1.1 mM octanesulfonic acid, 0.1 mM EDTA, and 9% acetonitrile (pH 3.0). The flow rate was 1 mL/min. The measurements were carried out using an LC4B electrochemical detector (BAS, United states) with a glass-carbon electrode (+0.85 V) against the Ag/AgCl reference electrode. Recording of the results was carried out using the Chrom 1.5 hardware and software complex (Ampersend, Russia). Calibration of the chromatograph was performed using a working standard mixture of substances at a concentration of 500 pmol/mL. To calculate the concentration of monoamines in the test samples, the "internal standard" method based on the ratio of peak areas in the standard and the sample mixture was used.

The concentrations of NA, DA, and its metabolites such as 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 3-methoxytyramine (3-MT), and 5-HT, as well as its metabolite 5-hydroxyindoleacetic acid (5-HIAA), were chromatographically determined. The data were subjected to statistical analysis using the one-way ANOVA test. A posteriori comparisons of the means were carried out using the criterion of the least significant difference, viz., LSD (ANOVA). In the control and exposed groups, the results that were obtained 90 days after exposure were compared with the data from day 30 after the exposure. To determine the directions of shifts in substance concentrations after exposure, the nonparametric Z-signs test was used. Differences were considered to be statistically significant at the confidence level of $p \leqslant 0.05$. The p-values from 0.05 to 0.1 were considered as a clear trend. The results of measurements were represented as the mean concentrations ± standard error of the mean.

RESULTS

The results that are shown in the table indicate the presence of certain differences between late changes in the control and exposed animals. In the prefrontal cortex of the control animals, significant differences between the different age groups were noted for the levels of four test substances: there was an increase in the concentration of NA, 5-HT, and 5-HIAA to 123.6, 124.5, and 126.8%, and a decrease in HVA levels to 48.4%, respectively. No statistically significant changes were observed in the other investigated parameters. In rats that were exposed to ^{12}C, the number of significant differences between the animals of different ages was smaller. A significant decrease in DOPAC level (to 43.3%) and an increase in 5-HT (to 121.3%) were observed. Thus, in the prefrontal cortex of the exposed animals, significant differences were observed for two of the studied parameters, while in the sham-exposed rats, they were observed for four of them. The differences in the late changes also included diverse modifications of the level of HVA in the control and exposed rats. In contrast to the control group, which had a significant decrease in the HVA concentration, in animals irradiated with ^{12}C ions, HVA levels increased to 138.9% but the difference was not significant. At the same time, together with a significant increase in the concentration of 5-HIAA in the control animals, in the group of exposed rats, this parameter did not significantly change with age; on the 90th day it was 99.6% of the 30-day level.

In the hypothalamus of animals that were exposed to ^{12}C ions, a unidirectional decrease in the concentrations of all analytes was observed with age: NA, to 62.3%; DA, to 43.3%; DOPAC, to 29.2%; HVA, to 21.6%; 3-MT, to 25.2%; 5-HT, to 83.7%; and 5-HIAA, to 78.9%. A significant change in DA, DOPAC, HVA, and 3-MT and a clear trend to change in NA were found. In the group of sham-exposed animals, 90 days after the exposure, a similar reduction of the levels of most of the substances and their ratios in comparison with values on day 30 was found: the NA concentration decreased to 56.1%; DA, to 44.6%; DOPAC, to 25.4%; HVA, to 19.2%; 3-MT, to 35.1%; and 5-HT, to 88.6%. Significant changes were found in NA, DA, DOPAC, and HVA. The 3-MT concentration had a tendency to change. In the hypothalamus of the exposed and control animals, the number of parameters that significantly changed with age was constant and equaled five. Analysis of paired comparisons using the Z-sign test revealed the non-random nature of the unidirectional decrease in the studied values in the exposed animals ($p \leqslant 0.05$). In the group of sham-exposed animals, no significant trends to unidirectional changes were found.

In the hippocampus of rats that were not exposed to radiation, a tendency to an increase in the concentration of 5-HIAA to 137.2% occurred, while this parameter in the exposed animals was reduced to 88.1% but the difference was not significant in the latter case. The opposite late changes in the control and exposed rats were also observed for DOPAC and HVA. In the sham-exposed animals, concentrations of DOPAC and HVA decreased to 81.1 and 58.5%, respectively, in the exposed group, in contrast, the DOPAC and HVA concentrations increased to 151.8 and 112.9%. However, no significant changes in these parameters were observed. The levels of other substances and their ratios changed unidirectionally with age, but in this case significant differences were not found as well.

In the striatum of the exposed rats, a significant increase in the concentration of 5-HT to 129.8% was found. In the control group, this value increased to 113.0% but the difference was not significant. The concentrations of other investigated substances changed insignificantly in both groups. In general, in the striatum, most of the parameters showed a similar pattern of change in the control and irradiated rats. Differences were observed only in DA and DOPAC, whose levels were virtually unchanged with age in sham-exposed animals and increased after exposure to ^{12}C ions to 109.6 and 108.6% respectively.

DISCUSSION

In our previous study [11], we investigated changes in the metabolism of monoamines that were observed at the first and second time points (30 or 90 days) after exposure separately. For this purpose, the data for each studied period from the control and irradiated groups were compared. On day 30, the most pronounced changes in the concentrations of monoamines and their metabolites were observed in the nucleus accumbens; smaller changes were found in the hippocampus and striatum. On day 90, significant changes remained only in the nucleus accumbens, whereas they became less noticeable in other structures, including the prefrontal cortex, hypothalamus, hippocampus, and striatum. In these studies, the superposition of radiation and the age factors was important in assessing the monoamine metabolism in later periods after the exposure. A number of neurochemical studies have indicated significant age-related changes in the cholinergic, catecholaminergic, and peptidergic regulation of synaptic transmission [12]. The functional activities of neurotransmitter systems vary over time, along with intensity of metabolic processes in general [13]. Most studies have shown an age-related decrease in the concentration, synthesis, and transport of neurotransmitters, but conflicting data on changes in the dynamics of these systems was obtained from individual brain structures [14–17].

Some studies suggest that the decline in the efficiency of DA-ergic neurotransmission may occur with age due to reduced DA transport in the striatum [18–21]. There are results that show an impairment of DA synthesis and metabolism [19, 20, 22, 23], as well as a

The concentrations of monoamines and their metabolites in different structures of the rat brain (nmol/mg tissue ± *SEM*) 30 and 90 days after irradiation with ^{12}C ions with the energy of 500 MeV/nucleon at a dose of 1 Gy. The age of animals is shown in parentheses.

Groups	Control			Irradiation with ^{12}C		
	30 days (3 months)	90 days (5 months)	*p*	30 days (3 months)	90 days (5 months)	*p*
Prefrontal cortex						
NA	1.10 ± 0.08	1.36 ± 0.04	**0.03**	1.25 ± 0.06	2.06 ± 0.53	0.27
DA	0.34 ± 0.03	0.58 ± 0.11	0.11	0.39 ± 0.04	0.51 ± 0.10	0.41
DOPAC	0.43 ± 0.09	0.29 ± 0.15	0.48	0.44 ± 0.06	0.19 ± 0.06	**0.04**
HVA	0.38 ± 0.07	0.19 ± 0.02	**0.04**	0.26 ± 0.05	0.36 ± 0.12	0.55
3-MT	0.09 ± 0.02	0.06 ± 0.00	0.21	0.09 ± 0.02	0.13 ± 0.05	0.62
5-HT	3.01 ± 0.20	3.75 ± 0.16	**0.03**	3.17 ± 0.11	3.84 ± 0.08	**0.01**
5-HIAA	1.66 ± 0.09	2.10 ± 0.14	**0.04**	2.02 ± 0.23	2.01 ± 0.07	0.98
Hippocampus						
NA	2.05 ± 0.25	1.57 ± 0.15	0.18	2.03 ± 0.18	1.45 ± 0.30	0.18
DA	0.79 ± 0.24	1.11 ± 0.57	0.66	0.39 ± 0.10	2.71 ± 1.91	0.31
DOPAC	0.37 ± 0.13	0.30 ± 0.08	0.70	0.43 ± 0.07	0.65 ± 0.21	0.39
HVA	0.59 ± 0.26	0.34 ± 0.13	0.48	0.70 ± 0.29	0.79 ± 0.24	0.84
3-MT	0.28 ± 0.14	0.19 ± 0.05	0.60	0.30 ± 0.05	0.21 ± 0.04	0.23
5-HT	2.69 ± 0.36	2.59 ± 0.13	0.82	3.85 ± 0.63	2.35 ± 0.50	0.14
5-HIAA	2.77 ± 0.19	3.80 ± 0.46	***0.10***	2.89 ± 0.33	2.55 ± 0.54	0.64
Hypothalamus				*		
NA	7.97 ± 0.69	4.48 ± 0.16	**0.002**	7.80 ± 1.17	4.85 ± 0.62	***0.08***
DA	3.19 ± 0.45	1.42 ± 0.20	**0.01**	2.92 ± 0.50	1.26 ± 0.10	**0.02**
DOPAC	0.92 ± 0.18	0.23 ± 0.07	**0.01**	0.59 ± 0.03	0.17 ± 0.04	**5×10^{-5}**
HVA	1.05 ± 0.28	0.20 ± 0.04	**0.03**	0.86 ± 0.23	0.19 ± 0.05	**0.03**
3-MT	0.38 ± 0.10	0.13 ± 0.03	***0.07***	0.35 ± 0.07	0.09 ± 0.03	**0.02**
5-HT	5.34 ± 0.58	4.73 ± 0.32	0.43	5.45 ± 0.35	4.56 ± 0.51	0.23
5-HIAA	3.19 ± 0.37	3.60 ± 0.37	0.51	3.69 ± 0.40	2.91 ± 0.24	0.18
Striatum						
NA	1.27 ± 0.64	0.60 ± 0.11	0.38	0.77 ± 0.30	0.43 ± 0.09	0.37
DA	44.73 ± 3.93	44.56 ± 3.85	0.98	47.83 ± 2.15	52.41 ± 4.05	0.40
DOPAC	2.94 ± 0.23	2.93 ± 0.16	0.97	2.98 ± 0.20	3.24 ± 0.18	0.42
HVA	2.31 ± 0.26	2.00 ± 0.20	0.44	2.14 ± 0.15	1.97 ± 0.16	0.52
3-MT	0.51 ± 0.07	0.40 ± 0.03	0.20	0.50 ± 0.04	0.47 ± 0.04	0.63
5-HT	3.54 ± 0.51	4.00 ± 0.22	0.48	3.06 ± 0.17	3.97 ± 0.20	**0.01**
5-HIAA	3.15 ± 0.18	3.61 ± 0.18	0.15	2.97 ± 0.20	3.32 ± 0.21	0.31

Bold italics ***(Italics)*** indicate a clear trend at $0.05 < p \leqslant 0.1$; bold underlines marks the significance level at $p \leqslant 0.05$. * The significant differences in the decrease according to the Z-sign test at $p \leqslant 0.05$ in the hypothalamus.

decrease in the number of DA-ergic neurons [24–26]. These disorders were observed mainly in the striatum, substantia nigra, putamen, caudate nucleus, amygdala, hippocampus, and hypothalamus. However, there is evidence of a decrease or lack of change in the levels of DA, DOPAC, and tyrosine hydroxylase activity in some structures of the rat brain, including the hypothalamus, hippocampus, and olfactory tract [20, 27–31].

Data on the NA-ergic system in different age groups vary for different structures. On the one hand, there is a decrease in the NA concentration in the limbic area, the medulla, pons, and spinal cord of older animals [23, 32]; however, in other structures, such as the hypo-

thalamus, striatum, mesolimbic system, and cortex, the opposite results were obtained [19, 21, 33, 34].

Ambiguous data on the dysfunction of the 5-HT system was obtained. Most of the experimental data show an age-related decrease in the concentration and transport of 5-HT in the striatum [21, 34, 35] and other limbic structures of the brain in rats [36, 37]. At the same time, in the hypothalamus, hippocampus, and frontal cortex, 5-HT metabolism increases or remains unchanged [29, 38]. In some experiments, a decline in the 5-HT uptake in rats with age was described [39]; however, other data showed no significant changes [40].

Many studies showed age-related changes in the glutamate and GABA-ergic systems of mammals and humans. The number of GABA-ergic neurons was reduced in the neocortex [41]; in the prefrontal cortex and cerebrospinal fluid, the level of GABA was decreased [42, 43]. The glutamate level decreased with age in the cerebral cortex, frontal and medial prefrontal cortex, hippocampus, and striatum [12]. This reduction is thought to be a consequence of changes in the metabolism of glutamate.

In this paper, we studied the effect of accelerated ^{12}C ions on the dynamics of changes in the NA, DA, and 5-HT systems in animals of different ages. The concentrations of monoamines and their metabolites were determined in four brain structures (the prefrontal cortex, hypothalamus, striatum, and hippocampus), which are actively involved in the control of many behavioral reactions of animals. The prefrontal cortex, hypothalamus, and hippocampus perform their functions by modifying the activities of the NA, DA, and 5-HT systems [44–48]. The striatum, which is the central structure of the basal ganglia, carries out motor control and controls complex behavior after receiving excitatory inputs from virtually all regions of the cerebral cortex [10]. The integration of glutamatergic synaptic information transmitted from the cortex is under the control of the nigrostriatal DA system.

The results that were obtained in our experiments show the effect of radiation on the early changes in the NA, DA, and 5-HT systems. Exposure of different brain structures to ^{12}C ions resulted in different changes in the concentrations of various analytes. In the prefrontal cortex of the exposed animals, the absence of a significant increase in the NA level 90 days after exposure may indicate a disruption of the normal process of accumulation of the neurotransmitter, which is usually observed in the studied age periods (3–6 months) [49]. However, a significant reduction in DOPAC concentration in the exposed rats compared to the controls indicates a rapid decrease in the activity of DA system after exposure to ^{12}C ions. This effect is probably associated with a decrease in the activity of the mesolimbic and nigrostriatal DA neurons.

These experiments showed that in the prefrontal cortex, radiation accelerated the reduction of the DOPAC level, which was observed in normal animals after reaching 3 months of age [49]. DA exchange in this structure in the exposed animals had differences in other parameters as well. In control animals, the HVA concentration significantly decreased with age, while no significant changes were found in the group of exposed animals. The observed differences can be evidence of a shift in the balance of DA metabolism towards catechol-O-methyltransferase (COMT) dependent pathways: DA $\rightarrow$ 3-MT and DOPAC $\rightarrow$ HVA, which may be a consequence of the inhibition of monoamine oxidase activity-A (MAO-A) after exposure to ^{12}C ions. Indirectly, this is confirmed by an increased DOPAC decline with age in exposed animals compared to the controls, and a (non-significant) increase in the concentration of 3-MT in the group that was subjected to radiation, unlike sham-exposed rats, where 3-MT levels dropped over time. The decrease in MAO-B activity may reflect the absence of later changes in 5-HIAA levels in exposed animals in comparison with the control group together with a significant increase in 5-HT concentration in both groups over time. These results may be the evidence of a disruption of the normal dynamics of the late changes, since in a number of studies, for example, in humans [50], an increased activity of MAO-B and no changes in the MAO-A activity in the prefrontal cortex with age was found.

In the hippocampus, which is the part of the limbic system and is involved in emotional responses, significant differences between the exposed and control group were observed only in the parameters of 5-HT metabolism. In the control group, an increase in the concentration of 5-HIAA at the age of 5 months in comparison with 3 months was consistent with the tendency that commonly has been found by other authors [49]. Exposure to ions led to a decrease in 5-HT metabolism, which appeared as the absence of significant changes in the level of 5-HIAA with time. In a similar manner to the prefrontal cortex, such differences may indicate the inhibition of MAO-B activity after exposure with age.

In the hypothalamus in the control and exposed animals, a similar decline of NA, DA, DOPAC, HVA, and 3-MT was found at the age of 2 months; however, analysis of the absolute values of the measured parameters indicated a delay in age-related changes in the exposed animals in four of these parameters (NA, DA, DOPAC, and HVA). These results indicate the active involvement of compensatory and regenerative processes in the hypothalamus at the late stages of post-radiation exposure, which, in turn, may be the cause of differences in the dynamics of early changes, which are expressed in the slowdown of the normal decline of neurotransmitters concentration over time. The hypothalamus is the structure where the food, drinking, and sexual centers are located. Therefore, the

observed differences in the NA, DA, and 5-HT systems may initiate behavioral changes related to these functions. A unidirectional decrease in all tested parameters was observed in the exposed animals but not in the control group. The analysis using the Z-sign test confirmed the non-random nature of these changes. Overall, our results show the ambiguity of radiation-induced changes in the hypothalamus, which apparently is a consequence of exposure to heavy ions with a comparatively low value of LET (10.6 keV/μm).

The striatum of the exposed animals had a pronounced tendency to age-related increase in the concentration of 5-HT along with a slight increase in DA and DOPAC. The analysis of the absolute values of the concentrations of 5-HT, DA, and DOPAC revealed no significant changes in these parameters in the group of sham-exposed rats. Since the normal increase in the concentration of 5-HT leads to increased release of DA in the striatum [51], these results may indicate the age-related activation of 5-HT receptors in response to radiation exposure. The severity of these changes, apparently, depends on the LET of particles; higher energy could possibly cause more pronounced effects that are associated with 5-HT-dependent change in the level of DA and its metabolites.

In these experiments, all of the investigated structures except the striatum had the same or a smaller number of significant late changes than in the control group. In the prefrontal cortex of exposed animals, only two of seven parameters significantly changed, while four of seven parameters changed in the control group. In the hippocampus no significant changes were found after the exposure to ^{12}C ions; one parameter changed in the control group. In the hypothalamus of the exposed and control rats, significant changes in five of seven parameters were found. We hypothesize that a decrease in the intensity of late changes in the studied time interval of 2 months is associated with the active functioning of compensatory and recovery mechanisms in the postradiation period. Realization of these processes may lead to the disruption of normal dynamics of monoamine metabolism that may appear not only as a reduction but also as an increase in the concentrations of the investigated substances over time. The dependence of the detected changes on the physical characteristics of the particles that were used is an important issue. It is possible that these effects are typical for radiation with relatively low LET (about 10 keV/μm), whose action is followed by the active work of compensatory mechanisms that provide eventual recovery of the damage. However, another scenario is possible at higher LET, when disorders induced by radiation are so severe that they cannot be compensated and result in functional changes that are manifested as a number of behavioral and cognitive disorders that have been observed in the experiments of other authors in different periods after irradiation [1, 3, 7, 52].

Considering our results, the investigation of the molecular mechanisms responsible for the recovery of monoamine metabolism after irradiation is of particular interest. Finding common mechanisms of the response of monoaminergic systems to ionizing effects is an important task, which may shed light on the causes of behavioral disorders and memory, the formation of negative emotional and motivational states of the irradiated animals.

In the study of compensatory processes, one important issue is the dependence of the efficiency of recovery on the age at which exposure occurred. In our experiments, young rats (7–8 weeks) with developing monoaminergic systems associated with the accumulation of neurotransmitters in some structures and active mechanisms of neurogenesis were exposed to radiation. These factors could contribute to the increased efficiency of recovery after radiation-induced damage in young animals.

Note that we did not find studies on the dynamics of late changes in monoamine metabolism in the rodent brain after exposure to ionizing radiation among the available scientific literature. Our results suggest that irradiation by ^{12}C ions at relatively low doses leads to modification of age-related dynamics of monoamine metabolism in young rats for at least 2 months. In the irradiated and control animals, the greatest differences in the temporal changes were observed in the prefrontal cortex and the hypothalamus, which may indicate the important role of these structures in the long-term effects of radiation on the central nervous system.

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