Study of Cognitive Parameters in the Post-radiation Period in White Mice

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Abstract

The aim of the study was to establish the dependence of memory formation processes and learning ability in gamma-irradiated white mice on the age and period after irradiation. The 1.5 year old male mice (Mus musculus) were used in the study. Mice whole-body irradiation with ^{137}Cs was performed at a dose of 5 Gy with a "Gamma-capsule-2". Spatial learning and memory formation were estimated in the elevated-type multi-way maze. Experiments were carried out after 48 hours and 30 days of irradiation for seven days (five trials each day). The number of errors (deviations from optimal trajectory) and total time for crossing the maze were calculated. The results of the study indicate that ionizing irradiation with total dose 5 Gy causes no significant spatial memory and behavior changes and aged-mice are more radio-resistant. Age-related radioresistance plays an major role in the early stage of post-radiation recovery. Though, the late radiation cognitive imparment marked by decreased verbal memory, spatial memory and attention has especially acute manifestation in young animals. These data match the literature data on the age dependence of radiation-induced cognitive dysfunction.

Keywords: Ionizing radiation; cognitive parameters; spatial learning; elevated plus maze.

1. Introduction

Ionizing radiation has multiple effects on brain functioning, behavior, and cognitive function. These changes are largely dependent on the radiation dose. Studies revealed that ionizing radiation affects the functions of the central nervous system what results in behavior and memory changes; these changes occur as a result of a direct effect of irradiation of the central nervous system and also indirect, as a result of response to irradiation of other organ systems [1]. The central nervous system is considered a radiosensitive system, and the degree of its dysfunction can be evaluated by electrophysiological, biochemical, and behavioral parameters. Impairments of these parameters can be observed after local, also total irradiation of the whole body [2].

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Nowadays, there is increasing evidence literature date that the response of the central nervous system to radiation is a continuous and interactive process. Particular attention is paid to apoptotic cell (neuronal) death, as well as, mechanisms of cells' damage and death induced by secondary injury [3].

Recent studies revealed cranial radiation therapy's impact on a wide range of brain functions resulting in cognitive and memory deficiency. Radiation-induced alterations develop with a dose-volume-dependent severity. After irradiation of the brain, detrimental effects develop, acute, early delayed, and late injuries are observed. High doses of ionizing radiation induce reactive gliosis, white matter necrosis, vascular abnormalities, which are irreversible and result in clinical symptoms [4]. Low doses can also induce a wide array of cognitive dysfunctions without any significant morphological changes [5].

Dysfunction of the central nervous system is manifested after a certain interval of time (months or years) of radiation exposure. Cognitive impairment is revealed in various degrees of learning difficulties, behavior changes, and memory deficits [6].

The presence of cognitive disorders after exposure to high dose irradiation have a connection to the hippocampus glial cells and proliferating progenitor cells in the subgranular zone of the dentate gyrus. This region is especially sensitive to ionizing radiation [7]. Doses of ionizing radiation above 1 Gy decreased the number of neural progenitor cells, which results in the arrested cell cycle, induces oxidative stress [8], and manifests as a cognitive disability, memory, and learning dysfunctions [9].

The aim of the study was to establish the dependence of memory processes and learning ability in gamma-irradiated white mice on the age and period after irradiation.

2. Materials and Methods

The experimental protocol was in accordance with the guidelines for care and use of laboratory animals as adopted by the Ethics Committee of the Tbilisi State Medical University (TSMU).

2.1. Animal care and maintenance

1,5 year-old male mice (Mus musculus), were obtained from the Vivarium of Tbilisi State Medical University. They were housed in animal cages, with room temperature maintained at 20^0-22^0C, relative humidity of 50-70%, and an airflow rate of 15 exchange/h. Also, a time-controlled system provided 08:00-20:00 h light and 20:00-08:00 h dark cycles. All mice were given a standard rodent chow diet and water from sanitized bottle fitted with stopper and sipper tubes.

2.2. Experimental design

After acclimatization for a week to laboratory conditions, the mice were divided into two different groups. The I control group of 1.5-old not irradiated mice, II experimental group – 1.5-old irradiated mice. Mice whole-body irradiation with ^{137}Cs was performed at a dose rate of 1,1Gy/min for the total dose of 5 Gy with a "Gamma-

capsule-2" (group II).

Spatial learning and formation of memory were estimated in the elevated-type multi-way maze.

The maze consists of 10 platforms (40x10 cm) fixed at a height of 25 cm. The motivation for movement along the maze under test conditions was to go back in the box-nest fixed at the end of the maze.

Experiments were carried out after 48 hours and 30 days of irradiation for seven days (five trials each day). Animals were placed in the start point facing the pathway of the maze. The familiarization session consisted of free exploration of the start and familiar arms for 10 min. On the first day, the experimenter helped the animal to find the optimal way leading to box-nest.

The number of errors (deviations from optimal trajectory) and total time for crossing the maze were calculated. Analysis of the obtained numerical data allowed us to estimate the dynamics of the learning process. Free passing in the labyrinth during 10-15 sec and the achievement of automated behavior was considered as a criterion of the complete learning process.

All experimental areas were wiped with 20% ethanol after each trial. All behavioral experiments were conducted during the light cycle after two hours of acclimation.

2.3. Statistical analysis

Statistical analysis of data was carried out using the "Statistical Package for Social Sciences (SPSS) for Windows (SPSS version 11.0). Data were reported as mean ± SD. A significant level of 0.05 was chosen to assess the statistical significance.

3. Results

Monitoring of spatial learning process of two animal groups in the elevated maze showed that animals of group I (control group of 1.5 year old mice) when placed in the maze for the first time, needed the help of the experimenter only in two trials of the first testing day. Later they independently opened up the new environment and demonstrated research activity. In animals of the I control group the average number of errors and mean time for crossing the maze, accordingly, was equal to 3and 2 (±0.5) min. Later animals independently opened up the new environment and the number of errors decreased and on the 6th and 7th days, mice found the shortest way leading to target and spent an average of 20 sec. Animals of the experimental II group showed decreased number of errors and on the 5th day of the experiment Improvement of the learning process and the total average time: mice reached the target-nest in 40 sec and the number of errors was the same compared to the control group. On the next 2-4th days the average number of errors decreased and the total average time became less than 3 minutes. Improvement of the learning process and the total average time needed for crossing the maze, determined by the middle part of the maze, significantly increased the rate of path recognition. Though on 6-7th days of the experiment the average number of errors and time gradually increased (Fig.1). The same results were obtained after one month of irradiation (Fig.2).
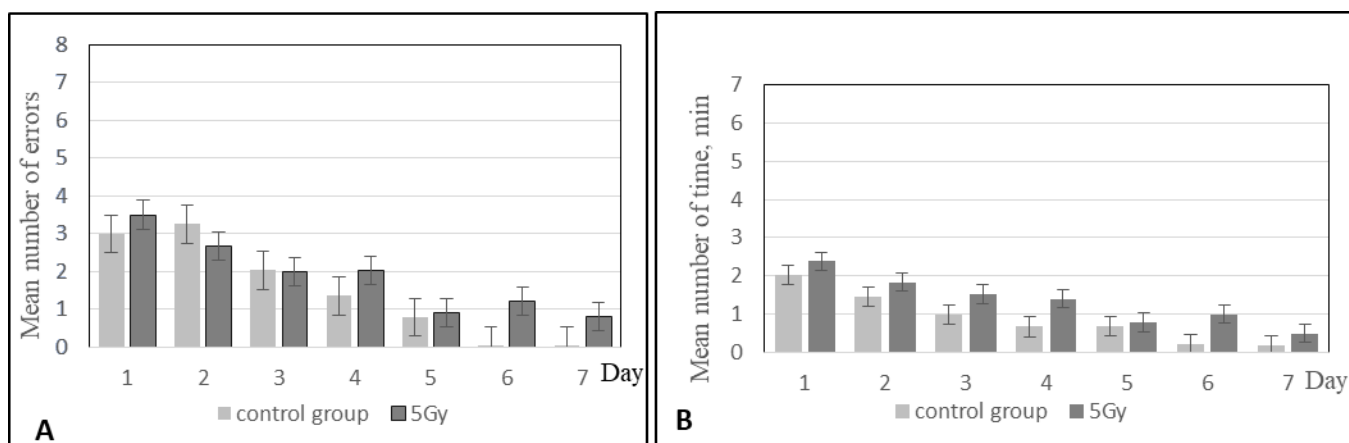
Figure 1: Effect of gamma-radiation on the cognitive parameters of 1,5-year old white mice after 48 hours of irradiation (during the 1-week period)

A - Average number of errors in control and experimental mice (groups I, II); B- Average time to cross the maze (min) in control and experimental mice (groups I, II).
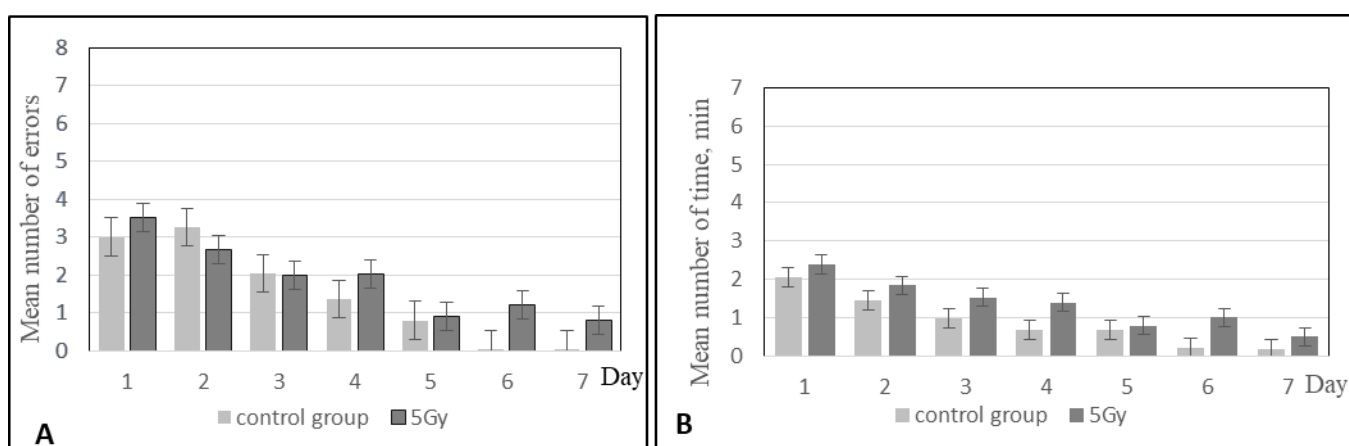

Figure 2: Effect of gamma-radiation on the cognitive parameters of 1,5-year old white mice after one month of irradiation (during the 1-week period).

A - Average number of errors in control and experimental mice (groups I, II); B- Average time to cross the maze (min) in control and experimental mice (groups I, II).

4. Discussion

The results of the study indicate that ionizing irradiation with total dose 5 Gy in the old (1,5-year-old) mice delaying effect of the radiation on the spatial learning process was insignificant. As seems from the results of our experiment, aged animals turned out to be more radioresistant. These data match the literature data on the age dependence of radiation-induced cognitive dysfunction; epidemiological studies revealed that the risk for cognitive dysfunctions is higher during prenatal and childhood irradiation [10].

5. Conclusion

Using a laboratory white mouse model, the results of the study indicate that that ionizing radiation exposure causes insignificant spatial memory and behavior changes in aged animals – aged mice turned out to be more radio-resistant. Age-related radioresistance plays an especially major role in the early stage of post-radiation recovery. Though, the late radiation aging effect formation is especially pronounced in young animals.

Acknowledgments

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