Modeling of Interplanetary Flight Factors: Dependence between Primates Cognitive Functions, Monoamine Metabolism and Individual Characteristics of Nervous System

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Mini-Review

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ABSTRACT

This article is a mini-review of a previously published in LSSR study of monkey cognitive and neurochemical changes after model impacts of deep space flight. After modelled microgravity and heavy ion irradiation animals show minor decline in cognitive functions and monoamine metabolism. The effect highly depends on individual characteristics of nervous activity: one of strong balanced type is much more resistant to model impacts. The results of this research on cognitive function demonstrate that the predominant element controlling changes in these functions is the morphological characteristics of the animals' higher neurotransmission. After the exposures, the strong balanced type of monkey efficiently maintained its cognitive abilities; however these abilities were impaired in weak unbalanced type animals. These alterations were accompanied by a reduction in monoamine levels and their metabolites as well as an increase in lymphocyte DNA DSB and chromosomal aberration yield.

Key words: Radiobiology; Monkey; Heavy ions; Microgravity; Neurochemistry; Cognitive functions

INTRODUCTION

Research on the effects of interplanetary spaceflight on the functions of the Central Nervous System (CNS) is extremely relevant due to planned missions beyond Earth magnetosphere (in particular, the Martian and Lunar missions). For such flights, assuming no protection of Earth's magnetosphere, impact of high-energy heavy ions is one of the main limiting factors. Combined with other adverse exposures, it can lead to disorders in the CNS functions undermining the astronauts' ability to perform duties. This, in turn, poses a real danger to the mission and to the crew itself [1-3].

It should be emphasized that in order to collect experimental data, allowing to estimate the probability of violations in the operator activity of astronauts, as well as to extrapolate such data to humans and assess the risk in terms of possible failures during a flight task, we have to model exact specific types of operator activity and research nervous and neurochemical mechanisms of the disorders in that activity. This way, we have to conduct experiments on monkeys that imitate close enough elements of operator activity, such as tracking an object on screen, manipulating objects with the use of joystick, predicting movement of on-screen objects, together with the study of the neurochemical mechanisms these processes are based on.

In our previous study, we investigated the neurobiological effects of two types of radiation characteristic of outer space - high-energy protons and ^{12}c ions in experiments on primates [4-6]. An extremely important, and at the same time, the least studied problem is the neurobiological effects of the combined impact of space radiation and the most significant non-radiation factor of space flight - microgravity. In a series of our papers, these effects were researched at all levels of CNS organization in small laboratory animals [7-10].

LITERATURE REVIEW

First of all, it should be observed that monkeys have extremely unique, Highly Active Nervous System characteristics (HAN). Therefore, it is crucial to consider their morphological characteristics while conducting neurobiological trials on monkeys. If it isn't done, actual results from experiments on monkeys may have more variance than changes brought on by exposure to the elements under study. The data collected on various animals should not be averaged for the same reason.

The background signs of the animal's behavior prior to exposure can be used as the best possible control. Indicators from the animals treated were used to assess the neurobiological effects of AOH and to eliminate any uncontrollable factors unrelated to ionizing radiation exposure.

The strength, balance, and flexibility of brain processes in many types of dynamic activity, including cognitive reactions to external stimuli and the process of learning various cognitive tasks, were among the typological traits of five monkeys. Methods that improved the excitability of cerebral cortex cells were used in the evaluation of the stimulation process strength. In evaluating the typological specifics the animals' reactions to outside stimuli such items of various sizes and shapes were taken into consideration. Others induced a natural defence reaction that evolved during evolution in response to danger signals like an object that resembled a snake, a toy's big eyes or an open mouth, or another monkey's scream in response to a presented object.

The reflex action weakened after 8-10 exposures of a conditioned reward stimulus, indicating the emergence of protective inhibition, or excitation process weakness. Later, the need to explore might grow. After 15-20 stimulus presentations, the reaction in some animals continued to be one of revulsion, a scream, or a grin; in weaker animals, it became one of passive defense (a scream and turning away from the irritating object). The animals displayed comparable responses as they learned a computer programme.

DISCUSSION

The dominant goal of this study was to investigate the effect of the synchronous combined impact of 1) Anti Orthostatic Hypokinesia (AOH), 2) long-term gamma irradiation and 3) irradiation of the head of monkeys with carbon ^{12}c ions on their cognitive functions, concentration of monoamines and their metabolites in the peripheral blood [11,12].

The experiments were carried out on 5 male rhesus monkeys (Macaca mulatta) aged 4 years weighing 5-7 kg: 3 experimental (monkeys No. 401, 365 and 558) and 2 control (monkeys No. 487 and 3834) animals. Animal maintenance rules, as well as the design of an experiment were approved by the IBMPRAS Commission on Biomedical Ethics [13].

Animals were exposed to AOH for 7 days: monkeys in restricting suits were fixed on tables inclined towards the head at an angle of 6 degrees. Irradiation by gamma rays at a total dose of 1 Gy was performed during the state of AOH on the 6th day of hypokinesia. Animals of experimental group were placed for 24 hours into a shielded room containing a GOBO-60 gamma-ray facility with a source of 137Cs (72 g-equiv. Ra).

The dose rate was 4.2 cGy/h. Irradiation of the animals' head by ^{12}c (455 MeV/n, 1 Gy) ions were carried out on the 5th day after recovery from hypokinesia at the U-70 facility of the Institute of High Energy Physics. The 'human-like' typological classification of monkeys is based on the strength, balance and mobility of nervous processes during various types of dynamic activity such as cognitive reactions to external stimuli and the processes of learning various cognitive tasks.

Animals were trained for 12 months by the method of the Psychological Test System (PTS), developed by American researchers and modified in IBMP, which imitates basic elements of operator activity such as joystick and cursor manipulation, object tracking, object selection etc [14,15]. Most of the tests are similar to computer gaming, allowing data collection on total and successful attempts and average time per attempt.

For neurochemical studies, animals were anesthetized *via* Ketonal and blood was collected from vena mediana cubiti before and after model impacts. 5 ml of blood was put into a plastic tube and centrifuged at 4°C for 20 min at 2500-3000 rpm (150-200G). Plasma for analysis (volume of 1 ml) was frozen in liquid nitrogen. The supernatant was analyzed by high performance liquid chromatography with electrochemical detection.

The results of testing 3 monkeys of the experimental group after head irradiation with carbon ^{12}C ions show a slight decrease in the activity of animals on the first day after exposure and then returning to the level that they had before two series of exposures (Figure 1)

Figure 1. Results of experimental group (different fill type corresponds to different animals).

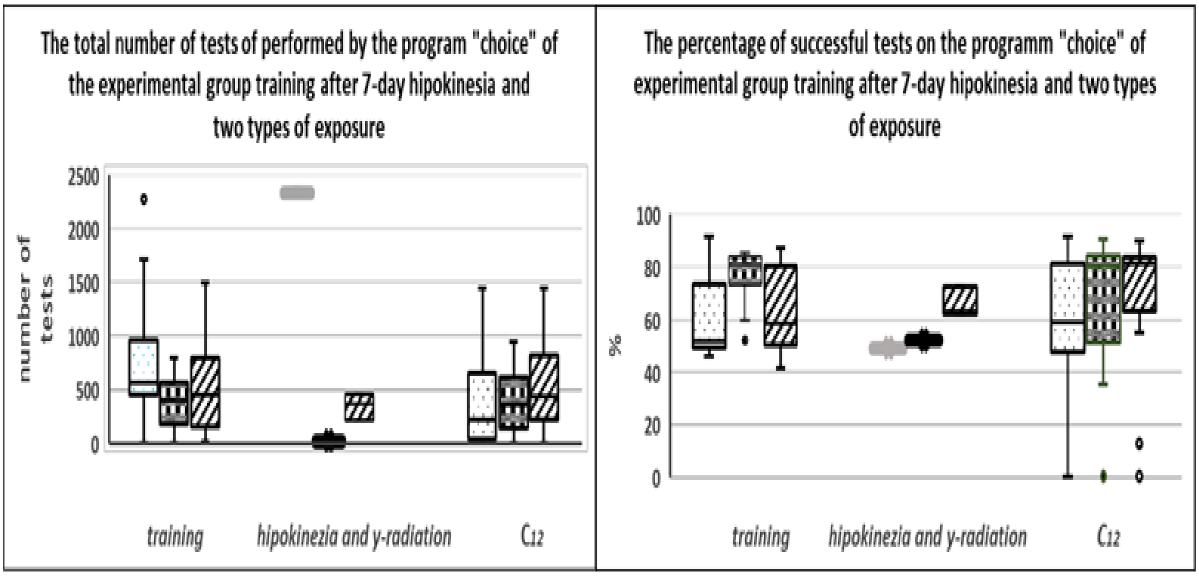
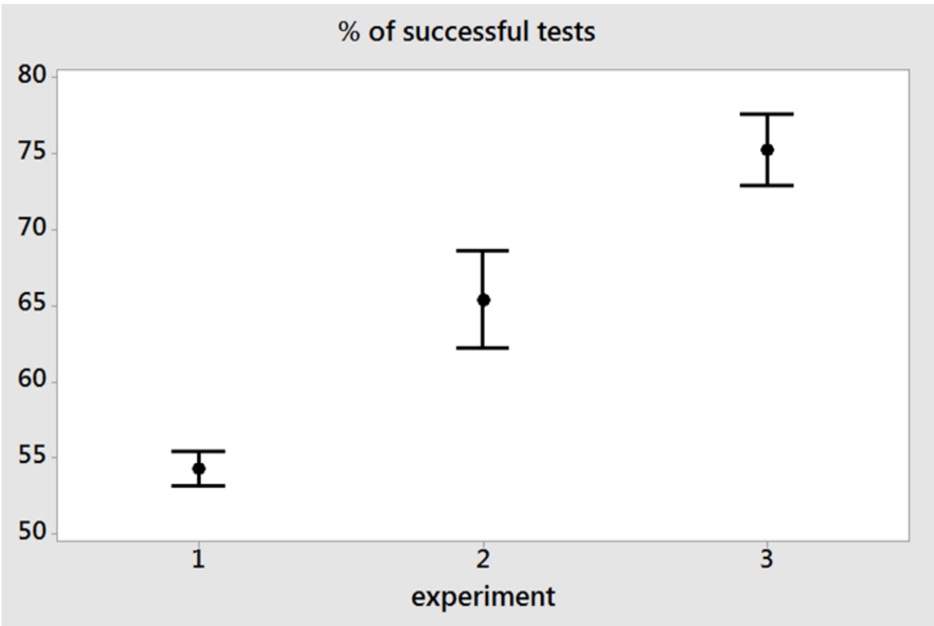


Figure 2 shows the variance analysis of the cognitive functions indicators for a monkey of strong balanced type, indicating a stable statistically significant increase in the number of successful attempts during the experiment.

Figure 2. Variance analysis of the cognitive functions for monkey No.3: (1) before impacts; (2) after AOH+γ-irradiation; (3) AOH+γ-irradiation+^{12}C.



Neurochemical studies result is shown in Table 1, where PC is a confidence level for irradiated animals related to control group, while P_{34} is a confidence level for samples taken 40 days after the exposure relative to these taken 34 h after the exposure.

Table 1. Monoamine and metabolite content 34 h and 40 d after the exposure.

Group	Control.	34 h	PC	40 days	PC	P34
L-DOPA	3.69 ± 0.35	2.82 ± 0.14	0.075	2.70 ± 0.24	0.117	0.799
NA	2.97 ± 0.29	2.52 ± 0.14	0.007	1.94 ± 0.17	0.019	0.428
A	4.49 ± 0.43	2.62 ± 0.64	0.339	3.30 ± 0.47	0.136	0.288
DOPAC	49.42 ± 7.16	21.85 ± 1.72	0.2	21.51 ± 1.20	0.061	0.102
DA	0.71 ± 0.12	0.48 ± 0.06	0.206	0.18 ± 0.04	0.06	0.418
HVA	0.02 ± 0.002	0.01 ± 0.001	0.0006	0.02 ± 0.002	0.821	0.368
3-MT	2.08 ± 0.15	1.00 ± 0.08	0.034	1.66 ± 0.12	0.511	0.093
5-HIAA	0.04 ± 0.006	0.02 ± 0.002	0.073	0.03 ± 0.002	0.09	0.654
5-HT	0.66 ± 0.1	0.57 ± 0.07	0.278	0.13 ± 0.05	0.09	0.515

CONCLUSION

Thus, the most important conclusion of our study is that the cognitive functions impairment after the combined effect of simulated microgravity and two types of ionizing radiation in primates is mostly related to change in dopaminergic system and motivation-emotion balance. Such balance highly depends on the typological characteristics of High Nervous Activity (HNA): individuals with a strong balanced or inhibitory type of HNA are capable of maintaining cognitive functions for a sufficiently high level after model impacts, while animals with weakly expressed plasticity of nervous processes or prevailing excitability and aggressiveness demonstrate significant, although temporary, decrease in cognitive functions. This, in turn, means that:

1) HNA type of future astronauts should become significant criteria of selection.

2) Some pharmacologic correction related to DA metabolism is probably, possible and must be investigated.

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