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CHANGE IN RADIO SENSITIVITY OF MICE UNDER EFFECT OF ROTATION

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Translation of "Izmeneiye radiochuvstvitel'nosti myshey pod vliyaniyem faktora vrashcheniya", Radiobiologiya, No. 2 (1979), pp 251-256

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16. Abstract

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CHANGE OF RADIOSENSITIVITY OF MICE UNDER THE EFFECT OF ROTATION

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Radiosensitivity of animals placed in slowly rotating chambers varied under the influence of the functional load on the vestibular analyzer. An increased radioresistance was registered in populations of the most radiosensitive mice. In populations of more radioresistant animals the gravitational load decreases the radioresistance.

In evaluating the ionizing radiation under space flight conditions /251* it is necessary to consider the effect of a whole number of extreme factors that modify the radiobiological effect. In particular, the change in the functional state of the vestibular analyzer under the influence of G-forces, vibrations and noise is one of the factors that affects the resistance of animals to the effect of ionizing radiation [1-5].

Taking into account that the Coriolis accelerations must emerge as an additional physical factor on orbital stations in the creation of artificial gravity, we studied the changes in radiosensitivity of animals under the influence of their preliminary keeping in slowly rotating units.

Material and Technique

Evaluation of the changes in the radiobiological effect under the influence of slow rotation was made in several series of experiments on

*Numbers in margin indicate pagination in original foreign text.

intact and labyrinthectomized mice of the SVA strain of more than 750 animals. Round-the-clock (with 2 hour break for mucking and feeding) or diurnal (lasting from 6 to 12 h) rotation of the animals was implemented on rotating units MVK-1 and MVK-2 [6]. The MVK unit (MVK--slowly rotating chamber) is a platform with diameter 2-2.2 m, on whose perimeter cages are installed with the animals. The platform together with the walls is rotated within a metal cylindrical volume (MVK-1) or located in a darkened room (MVK-2). In the latter case artificial illumination is created on a plan of 12 h of light and 12 h of darkness, and to remove the optokinetic irritations during the rotation the cages in which the animals are kept are glued with light paper. The MVK-1 platform was rotated with a velocity of 40°/s, MVK-2--45°/s. The Coriolis accelerations of small, practically indefinable amount emerged here during free movements of the animals in the cage and movements linked to eating. Labyrinthectomy of the mice was done under ether from two sides by irrigating the middle ear with a 10% solution of monoiodoacetic acid [7]. For this a thick syringe needle with dull point perforated the tympanic membrane and into the middle ear from the one and then the other side;the indicated solution was poured in and immediately suctioned out. Already in 30 min. the animals displayed the first signs of loss of the labyrinth function; a pronounced striving to keep footing and swinging ataxic motions while searching for footing. With time these phenomena were attenuated, the animals began to move more confidently; however, the ataxia was maintained to a certain degree even in later periods of observation. The death rate of the labyrinthectomized mice was 20%. The death of the main mass of animals who were operated on was noted in 7-10 days after the operation. After 20 days the population of the operated-on animals remained unchanged. The labyrinthectomized animals entered the experiment no earlier than in 40 days after surgery. The animals were irradiated from a γ-source Co^{60} and /252 Cs^{137} in doses of 675, 800 and 850 R. These doses were previously defined as $LD_{50/30}$ with power of radiation 400, 37 and 12.7 R/min. respectively.

Besides determination of the resistance of mice to radiation effect a study was made of the reaction of the system of hemopoiesis to the action of the actual factor of rotation and to irradiation of the preliminarily

rotated animals. A study was made of the quantity of formal elements of the blood and the number of karyocytes of the bone marrow in the femur, thymus and spleen according to the plan presented in publication [8]. The state of the stem hematopoietic cells of the marrow was also studied by evaluating their colony-forming ability by the method of exogenous clone-formation [9]. The effect of the rotation factor on the indices of the hemopoietic system was studied in dynamics on the second, ninth, 14th and 20th days of rotation, while the radiation reaction of the hemopoietic system--on the fourth and 15th days after acute irradiation in a dose of 675 R of animals, also preliminarily rotated for the indicated periods. The radiosensitivity KOE of the marrow in the control and rotated animals was determined by irradiation of it in doses of 200, 350 and 500 R. No less than 7 animals were used for each period of study for all the hematological indices. The material was statistically processed.

Results and Discussion

The scheme of the experiments and the death rate of the experimental animals are presented in the table, from which it is evident that the placing of mice in a slowly rotating chamber for a period of 2 to 20 days before irradiation results in a change in their radioresistance. The changes in the latter depend on the initial resistance of the animals to the effect of ionizing radiation. We obtained an idea about the initial radioresistance of different populations of animals after irradiation and evaluation of the radiation reaction of the control groups that were kept for a certain time in normal conditions of a vivarium. It was found that the radioresistance of mice in the same strain SVA fluctuated in our experiments depending on the sex, weight, time of study, conditions of maintenance, i.e., on the physiological condition of the animals taken from the nursery, in considerable limits. Strictly, the $LD_{50/30}$ for the employed sources of irradiation was /253
worked out as the mean of a number of previously conducted experiments in which the death rate of the animals fluctuated in limits of 20-80%. Therefore to reveal the shifts in radiosensitivity under the influence of Coriolis accelerations we divided the animals received at different times from the nursery into groups that were equal in numbers, part of which subsequently were exposed to the rotation factor, while irradiation of the

rotated and control animals was carried out simultaneously, in the same dose on the expiration of the period of rotation of the experimental groups. In the populations of mice that normally are more resistant to the radiation effect,

DEATH RATE OF INTACT AND LABYRINTHECTOMIZED MICE OF SVA STRAIN BY 30TH DAY AFTER RADIATION EFFECT IN GROUPS OF CONTROL AND PRELIMINARILY ROTATED ANIMALS

Series	Groups	No. of animals	Conditions of maintenance	Length of rotation		Dose,R; power of dose,R/min	Death rate, %
				days	hours		
1	Intact mice of SVA strain,	30	without rotation	0	0		87
	males,average	26	daily rotation	2	24		0
	weight 22 g	30	" "	9	94	675;400	3
		30	" "	14	158		3
		30	" "	20	234		13
2	Intact mice of SVA strain,	20	without rotation	0	0	675;400	40
	males, average weight 18 g	20	daily rotation	2	26		95
3	Intact mice of SVA strain,females,average weight 20 g	37	without rotation	0	0	850;12.7	46
		41	24-hour rotation	2	44		90
4	Intact mice of SVA strain,females,mean weight 18 g	20	without rotation	0	0	800;37	70
		20	24-hour rotation	20	440		7
5	Labyrinthectomized mice of SVA strain, males,mean weight 18 g	16	without rotation	0	0	850;12.7	100
		16	24-hour rotation	2	44		100
6	Labyrinthectomized mice of SVA strain females,mean weight 18 g	16	without rotation	0	0	800;37	45
		16	24-hour rotation	20	440		33

rotation resulted in an increase in the radiosensitivity (table, series 2,3). On the contrary, in the populations of radiosensitive mice the gravity load produced an increase in the radioresistance (series 1,4). Of especially great importance is the fact that the change in radioresistance was possible only in groups of intact mice whose vestibular apparatus is in a state to react to the functional load, while irradiation of the rotated but labyrinthectomized animals did not alter their radiosensitivity (series, 5,6).

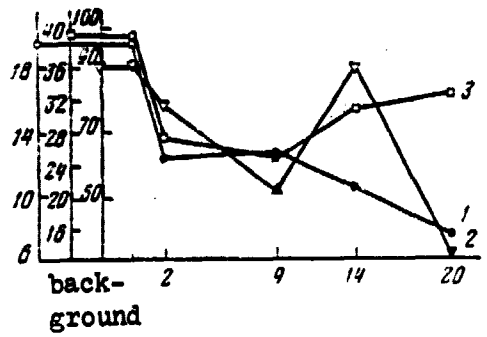

Figure 1. Change in Hematological Indices in Mice of SVA Strain Depending on Length of Their Rotation
On x-axis--length of rotation, days; on y-axis--1--number of leukocytes thous/mm^3; 2--thymocytes, million/mm^3; 3--myelokaryocytes, million/mm^3. Dark symbols--reliable difference from control.

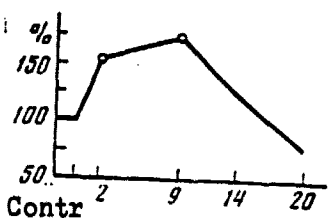

Figure 2. Change in Number of Stem Cells in Bone Marrow of Mice Depending on Duration of Rotation
On x-axis--duration of rotation, days; on y-axis--content of colony-forming units, % of initial amount--10^5 of introduced cells of bone marrow.

The change in hematological indices in the mice depending on the duration of their rotation is given in fig. 1. Figure 2 shows that a reliable increase in the number of stem cells of the bone marrow was noted on the second and ninth days of rotation of the animals. Thus, in the process of rotation according to a number of indices noticeable shifts were obtained that indicate the undoubted effect of the factor of rotation and Coriolis accelerations on the hemopoietic system.

Acute irradiation in a dose of 675 R is a sufficiently powerful pathogenetic factor that produces the first time a single-type reaction with respect to magnitude manifest as elimination of the cellular elements in the hemopoietic system regardless of the duration of preliminary rotation of the animals. However, changes in the hematological indices on the 15th day after radiation effect (fig. 3) in the period of restoration of the radiation

damages indicates that the initial functional state of the hemopoietic system that is altered under the influence of rotation determines the course of its restorative processes. Thus, the reaction of the post-radiant restoration of the number of leukocytes in the preliminarily rotated animals is directly proportional to the length of action of the vestibular load. The /254
rate of restoration of the number of thymocytes and myelokaryocytes is also considerably higher in the preliminarily rotated animals. As is apparent from figure 4, the survival rate KOE during irradiation in a dose of 200 R of the bone marrow taken from mice who were rotated for 9 days was increased by 30% as compared to the control. Large doses of radiation effect nullify the difference in the reactions of survival rate KOE in the preliminarily rotated animals.

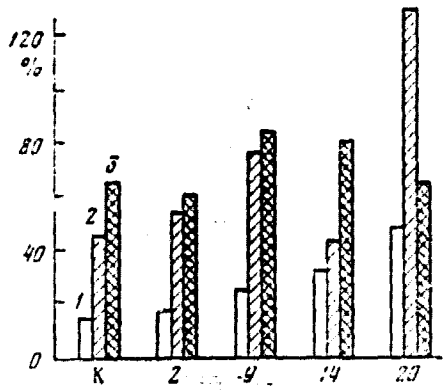

Figure 3. Post-radiation (on 15th day) Changes in Number of Leukocytes (1), Thymocytes (2) and Myelokaryocytes (3) in Mice Exposed to Preliminary Effect of Rotation Factor On x-axis--length of rotation, days; on y-axis--magnitude of indices, % of initial values

Thus, a study of mice in the SVA strain of the magnitude of hematological indices and state of the stem hematopoietic cells in response to the effect of Coriolis accelerations during slow rotation for 2,9,14 and 20 days and subsequent acute irradiation showed the dependence of the reactions of the hemopoietic system on the duration of the effect on the animals of the rotation factor. In the given case the functional load on the vestibular analyzer possesses the main sign of the stress irritant. By changing the total reactivity of the organism it produces deep shifts in the functioning of the hemopoietic system manifest in a decrease in the number of leukocytes in the blood, thymocytes, number of nuclei-containing cells of the bone marrow, in an increase in the colony-forming ability of the bone marrow, and in an increase in the reactivity of the system of hemopoiesis to the radiation effect.

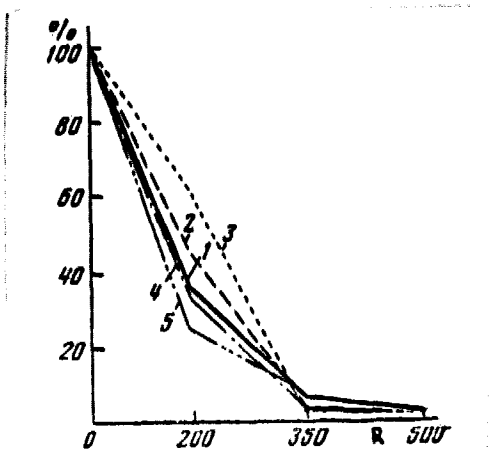

Figure 4. Colony-forming Ability of Stem Cells after Irradiation of Bone Marrow Taken from Mice of SVA Strain Exposed to Preliminary Rotation
On x-axis--dose of irradiation, R; on y-axis--number of colony-forming units, % of initial level; 1--control; 2--2 days, 3--9 days, 4-14 days, 5--20 days of rotation.

Recently the stress nature of altered gravity effects such as G-force or weightlessness has been clearly shown [10]. After 7-day exposure of the mice at 2 g a reduction was noted in the number of lymphocytes, thymocytes and splenocytes, drop in weight of the thymus and spleen. Analogous changes were observed also after a 22-day flight of rats on the satellite "Cosmos-605" [10,11]. The changes we noted in the system of hemopoiesis that emerged as a result of the lengthy effect of small Coriolis accelerations, apparently, can also refer to the category of gravity stress. The currently /255 available information about changes under the influence of slow rotation in the general reactivity of the organism to the effect of ionizing radiation is limited. It indicates the primary increase in the radioresistance of animals rotated before irradiation for 10 days with velocity of 21°/s [4]. In our experiments we always obtained a shift in the radiosensitivity in the groups of rotated animals. It is true that the direction of this shift depended on the initial level of reactivity of the population of animals used for the experiment. Among the radiosensitive mice whose initial level of sensitivity to the radiation effect exceeded the 50% death rate we found an increase in the survival rate, in certain cases almost to 90%. On the contrary, in the populations of radioresistant animals whose death rate under the assigned conditions of irradiation in the semi-lethal dose did not exceed 50% the vestibular load induced a reduction in the radioresistance. The unique effects that we obtained of "scissor" in the

shifts of animal radioresistance, apparently, are a phenomenon of the same order as those observations which indicate that any changes in the radiosensitivity of animals are possible only in the limits of their daily oscillations [12].

The absence of differences in the radiant reactions in the labyrinthectomized mice indicates that shifts in the radiosensitivity of the experimental animals that occur after a certain period of their rotation occur as a result of the change in the functional state of the vestibular analyzer under the influence of the rotation factor. It is known that the stay of animals and man in a slowly rotating chamber produces a shift in the functional state of the organism of the animals and development of the symptom complex motion sickness in man [6,13,14]. Here stimulation of the vestibular analyzer is the initial link in the chain of reactions of motion sickness. It results in the state of excitation of definite regions of the cortex and subcortical autonomic centers, which also govern the development of the autonomic reactions of the symptom complex of motion sickness. The engagement of the hypothalamus also determines the beginning of the general adaptation reaction of the organism to the unusual stimulant, a reaction that is implemented through the system of hypophysis-adrenal cortex, and directed to the achievement of the organism's adaptation to the effect of the unfavorable factor. With systematic training of the vestibular analyzer by different rotations and the effect of accelerations in rats an increase was observed in the absolute and relative weight of the adrenals [5]. Apparently, not only the super-optimal irritation of the vestibular analyzer by the centrifugal accelerations, but also the long effect of small Coriolis accelerations, that have, as we showed in the example of reactions of the hemopoietic system, a stress nature, are capable of altering the reactivity of the organism. The changes that emerge here in the state of the cardiovascular system and other autonomic reactions of motion sickness create a background on which the effect of the ionizing radiation can induce modified radiobiological effects.

Thus, from an analysis of the given material it follows that the prolonged effect of slow rotation with small centrifugal Coriolis

accelerations is addressed in the first place to the vestibular analyzer. Those shifts in the functional state of the organism that emerge under the unusual conditions of the effect of gravity during slow rotation are vestibulo-autonomic disruptions in the symptom complex of motion sickness. The vestibular load that has the nature of a stress irritant, activates the adreno-corticotropic mechanism for adaptation of the organism to the effect of unfavorable factors of the environment, increasing the overall nonspecific resistance of the organism. Changes in the radiosensitivity of the experimental mice emerge as a result of the inclusion of the adaptation reaction in the response to the effect of the vestibular load. Here /256
oscillations of different direction in the radiosensitivity of preliminarily rotated animals are possible that are governed by the different background of the initial reactivity of the organism. A moderate prolongation in the period of effect of the vestibular load (up to 10-20 days) increases the reliability of its use as a factor that increases the radioresistance of the animals.

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