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A. A. Kostina https://orcid.org/0000-0001-7731-8015
G. F. Stepanov https://orcid.org/0000-0002-8242-8689
A. A. Dimova https://orcid.org/0000-0002-3355-6799
Ye. Ye. Pelekhovych https://orcid.org/0009-0000-6349-6507

THE ROLE OF THE BLOOD CELL COMPONENT IN THE FORMATION OF MUSCLE DYSFUNCTION IN IRRADIATED OFFSPRING BORN TO ANIMALS EXPOSED TO DIFFERENT RADIATION DOSES

Odesa National Medical University, Odesa, Ukraine

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Radiation-induced hematological and metabolic disturbances remain insufficiently understood, particularly in the offspring of irradiated parents, despite their potential contribution to tissue dysfunction and long-term post-irradiation effects.

The aim of the work – to investigate the role of the blood cell component in the formation of muscle dysfunction in irradiated offspring born to animals irradiated at different doses.

Materials and methods. 1-month-old Wistar rats obtained from parents irradiated at 0.5 Gy and 1.0 Gy were subjected to single total-body γ-irradiation at 1.0 Gy. Hematological indices, activities of pyruvate kinase and lactate dehydrogenase, and levels of pyruvate and lactate were determined in peripheral blood, myocardium, and skeletal muscle using standard biochemical and spectrophotometric methods.

Results and discussion. Total-body γ-irradiation at 1.0 Gy reduced hemoglobin concentration and erythrocyte count in the offspring, limiting oxygen supply to tissues. Metabolic disturbances were dose-dependent and most pronounced in the progeny of animals irradiated at 1.0 Gy, showing a marked decline in pyruvate kinase activity in skeletal muscle, while myocardial changes were minor. Concurrent increases in lactate dehydrogenase activity and in lactate and pyruvate levels elevated the lactate/pyruvate ratio, indicating suppression of oxidative phosphorylation and a shift toward anaerobic glycolysis.

Conclusions. Offspring of animals irradiated at different doses exhibit dose-dependent hematological deficits and metabolic shifts, including reduced erythropoiesis, impaired oxygen-transport capacity, inhibition of substrate-level phosphorylation, and activation of anaerobic glycolysis, which may contribute to radiation-induced muscle dysfunction.

Keywords: total-body γ-irradiation, offspring of irradiated animals, blood cells, pyruvate kinase, lactate dehydrogenase.

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А. А. Костіна, Г. Ф. Степанов, А. А. Дімова, Є. Є. Пелехович
РОЛЬ КЛІТИННОГО КОМПОНЕНТА КРОВІ У ФОРМУВАННІ М'ЯЗОВОЇ ДИСФУНКЦІЇ ОПРОМІНЕНИХ НАЩАДКІВ, НАРОДЖЕНИХ ВІД ОПРОМІНЕНИХ У РІЗНИХ ДОЗАХ ТВАРИН
Одеський національний медичний університет, Одеса, Україна

В експериментальному дослідженні на 1-місячних щурятах, отриманих від тварин, опромінених дозами 0,5 та 1,0 Гр, та підданих одноразовому тотальному γ-опроміненню в дозі 1,0 Гр, було з'ясовано значення клітинного складу крові у формуванні м'язової дисфункції. Встановлено, що тотальне γ-опромінення дозою 1,0 Гр призводить до зменшення кількості еритроцитів і рівня гемоглобіну в периферичній крові, що обмежує забезпечення тканин киснем. Це, зі свого боку, пригнічує процеси субстратного фосфорилювання в м'язовій тканині 1-місячних щурят, народжених від опромінених у різних дозах тварин. Вираженість метаболічних порушень виявилася залежною від дози опромінення дорослих організмів, де опромінення дозою 1,0 Гр батьків призводить до вираженого зниження активності піруваткінази у скелетних м'язах їхніх нащадків, а ніж у міокарді, у яких спостерігали лише незначне зменшення ферментативної активності. На тлі ослаблення окисного фосфорилювання це зумовлює дефіцит енергії, яка формується шляхом анаеробного гліколізу, що критично важливо для збереження функціональної активності м'язів у стані гіпоксії.

Ключові слова: тотальне γ-опромінення, нащадки опромінених тварин, клітини крові, піруваткіназа, лактатдегідрогеназа.

Introduction

The study of the effects of ionizing radiation is of great importance due to the global prevalence of radiation exposure factors [1; 2].

The widespread use of atomic energy for peaceful purposes – in energy production, medicine, agriculture, industry, and space exploration – alongside the deployment of nuclear weapons in military conflicts, poses a serious potential risk to both current and future generations. It is worth emphasizing that the number of individuals exposed to sources of ionizing radiation will continue to grow [3].

In the context of prolonged technogenic impact on the biosphere, the study of chronic low-intensity radiation exposure has gained particular relevance. Under conditions of large-scale environmental radiation contamination, assessing its biological effectiveness is a priority in modern research. It is known that populations living in areas with elevated radiation backgrounds exhibit a steady increase in overall morbidity, indicating the long-term effects of low-dose ionizing radiation on the body [4].

Moreover, literature data indicate that most participants in the Chernobyl accident received such doses of radiation. Current research confirms the high genetic impact of both acute and chronic low-dose radiation exposure [5].

Unlike muscle tissue, which is considered radioresistant [6], blood cells are characterized by high metabolic activity and rapid division, making them among the first to respond to ionizing radiation, even at low doses [7; 8].

Furthermore, under single or especially prolonged exposure to low doses of ionizing radiation, the mechanisms of radiation-induced changes in the hematopoietic system are considerably more complex than those observed after sublethal or lethal exposures and remain insufficiently understood. Accumulating experimental data under conditions closely resembling those in radiation-contaminated regions may contribute to a deeper understanding of these processes [9; 10].

When offspring born to animals exposed to even minor doses of ionizing radiation are subjected to irradiation, it is logical to assume the development of more profound changes in hematopoietic system parameters.

The aim of the work is to investigate the role of the blood cell component in the formation of muscle dysfunction in irradiated offspring born to animals irradiated at different doses. This knowledge can facilitate the development of preventive, therapeutic and rehabilitation measures for muscle dysfunctions caused by ionizing radiation in irradiated offspring.

Materials and Methods

The studies were conducted on 1-month-old white rats weighing 30–32 g, Wistar line, maintained on a standard labortory diet. The young rats had free access to food and water and were kept under standard housing conditions with a natural 12-hour light–dark cycle, 60% humidity, and a temperature of (22 ± 1) °C. All procedures involving the animals were performed in accordance with institutional and international guidelines for animal care [11]. The assessment of prenatal loss was not performed.

The animals were divided into groups as follows:

Group 1 – 1-month-old rats born to intact animals (the control group).

Group 2 – 1-month-old rats born to animals irradiated with a dose of 0.5 Gy, subsequently exposed to a 1.0 Gy dose.

Group 3 – 1-month-old rats born to animals irradiated with a dose of 1.0 Gy, subsequently exposed to the same dose.

Each group consisted of 10 animals.

For the experiment, 1-month-old rats obtained from animals irradiated with a dose of 0.5 and 1.0 Gy were subjected to total single gamma irradiation with ^{60}Co in the morning after an overnight fast using the “Agat” telegamma therapy unit at a distance of 75 cm from the radiation source, dose rate of 0.54 Gy/min and absorbed dose of 1.0 Gy.

For biochemical studies, the animals were euthanized under propofol anesthesia (intravenous, 60 mg/kg). After dissection, blood was collected and the heart and anterior thigh muscles were excised. Tissue preparation was conducted according to standard protocols [12]. To determine the content of biosubstrates in the tissues, the samples were immersed in liquid nitrogen, deproteinized with 0.6 N perchloric acid, and homogenized. The protein precipitate was separated by centrifugation for 15 minutes at 3000 rpm.

For the biochemical assays, the mitochondrial supernatant and blood from the experimental animals were used.

The study focused on determining hematological parameters, enzyme activity and concentrations of metabolites involved in aerobic and anaerobic metabolism pathways, as well as oxidative and substrate-level phosphorylation in different muscle types of irradiated rats born to mature animals irradiated at different doses.

To assess blood cellular elements and serum protein content, blood samples were collected from the tail vein. This method allowed for longitudinal monitoring of the same animals over a 30-day observation period [13]. The proposed technique for determining blood protein levels offers the advantage of minimal invasiveness: it requires only microvolumes of blood, easily obtained from the tail vein so there was no need for euthanasia. This enables objective tracking of the biological status (cellular elements, protein levels) in the same animals throughout the experiment, which is crucial for studying pathological processes. The quantitative composition of blood cells was determined using an automated hematology analyzer (Mindray BC-5800, China).

To determine enzyme activities and metabolite levels, the animals were removed from the experiment one day after irradiation at a dose of 1.0 Gy.

The principle of pyruvate kinase activity determination is based on the conversion of phosphoenolpyruvate to pyruvate in the presence of ADP. Subsequently, pyruvate is reduced to lactate by lactate dehydrogenase (LDH) in the presence of reduced NAD (NADH), during which NADH is oxidized [14]. Pyruvate kinase activity was expressed in nmol of pyruvate per mg of protein per minute of incubation.

The principle of the method for determining lactate dehydrogenase activity is based on the reduction of pyruvate to lactate in the presence of reduced NAD [15]. LDH activity was expressed in μmol NADH consumed per mg of protein in the sample per 1 min of incubation.

The principle of the method for determining lactate and pyruvate content is based on the enzymatic reaction catalyzed by LDH in the presence of either the oxidized or reduced form of NAD. The accumulation or depletion of NADH was recorded spectrophotometrically at 340 nm against a control without tissue extract, with results expressed in μmol per 1 g of tissue [14]. The protein content in the samples was determined using the biuret method.

The obtained data were processed using parametric and non-parametric statistical methods. Statistical analysis was performed using the "IBM SPSS Statistics 20" software package. The minimum level of statistical significance was set at $p < 0.05$.

Research results and their discussion

The study results indicate that as early as one day post-irradiation, the offspring born to animals irradiated with 0.5 Gy and subsequently exposed to an additional 1.0 Gy dose exhibited a decrease in hemoglobin levels and red blood cell count, along with an increase in platelets, lymphocytes, reticulocytes, and a statistically significant rise in leukocytes in the peripheral blood ($H = 22.068$; $df = 5$; $p < 0.05$) compared to intact animals.

On the third day following irradiation, a further statistically significant decrease in hemoglobin was observed compared to the control group ($H = 34.483$; $df = 5$; $p < 0.05$). Concurrently, a trend towards a decrease in the number of erythrocytes, reticulocytes, leukocytes, and platelets was noted, while the lymphocyte count increased. Although the number of erythrocytes, reticulocytes, and platelets remained below control levels, the leukocyte count, despite declining, still exceeded that of intact rats.

By the seventh day post-irradiation, a significant reduction in hemoglobin concentration was observed ($H = 34.483$; $df = 5$; $p < 0.05$), against a background of non-significant decrease in erythrocytes, reticulocytes, and platelet counts. A similar trend was observed for leukocytes and lymphocytes, however, their levels still exceeded control values by 2.5% and 11.2%, respectively.

By the 15th day, a significant reduction was observed in most blood cell counts. An exception was the leukocyte count, which remained somewhat elevated, while the lymphocyte proportion was 34.4% higher than in the controls ($H = 29.564$; $df = 10$; $p < 0.01$).

By day 30, a partial restoration of the blood cell composition was noted; however, most parameters remained lower than those in the intact animals, with the exception of platelets, the level of which was slightly elevated compared to the non-irradiated animals.

More profound changes in hematological parameters were observed in the offspring born to animals irradiated with a dose of 1.0 Gy and subsequently subjected to the same dose of irradiation.

In the offspring of animals irradiated with 1.0 Gy, following re-irradiation with the same dose, pronounced changes in hematological parameters were recorded (Fig. 1).

Within 1 day, hemoglobin levels decreased by 1.7% compared to the control, and erythrocyte count was 7.6% lower. At the same time, a statistically significant increase in leukocytes by 1.35 times ($H = 54.961$; $df = 10$; $p < 0.05$) was observed, while lymphocyte levels decreased by 10%.

By day 3, the decrease in hemoglobin had progressed and reached 89.5% of the intact level; the erythrocyte count decreased by 9.5%, and reticulocytes and platelets decreased by 10% and 7.5%, respectively. Meanwhile, leukocyte levels remained elevated by 8% compared with the intact animals, while lymphocyte content increased by 7.5% compared to intact animals.

By the seventh day, hemoglobin concentration reduced by 13.4% ($H = 54.625$; $df = 5$; $p < 0.001$), and reticulocyte and platelet counts also declined slightly. Erythrocyte count decreased by 17.8% ($H = 40.146$; $df = 10$; $p < 0.001$). Leukocyte counts decreased by nearly 11%. Meanwhile, lymphocyte levels were 5.5% higher than in intact animals.

On day 15, minimal values were recorded, specifically: hemoglobin decreased by 32.3% ($H = 94.056$; $df = 10$; $p < 0.001$), erythrocytes by 42.5% ($H = 40.146$; $df = 10$; $p < 0.001$), leukocytes by 27.3% ($H = 54.961$; $df = 10$; $p < 0.01$), platelets by 28.6% ($H = 40.506$; $df = 10$; $p < 0.001$), and lymphocytes by 21.6%.

By day 30, partial restoration of the blood cell composition was observed; however, hemoglobin levels remained reduced by 17.5% compared to controls ($H = 94.056$; $df = 10$; $p < 0.001$), erythrocytes by 27% ($H = 40.146$; $df = 10$; $p < 0.001$), and platelets by 32% ($H = 40.506$; $df = 10$; $p < 0.001$). These changes were accompanied by a non-significant decrease in leukocyte and lymphocyte counts, whereas the reticulocyte count was slightly elevated relative to the control group.

The decrease in hemoglobin and erythrocyte content in the peripheral blood of offspring born to animals irradiated at different doses, which were exposed to irradiation at a dose of 1.0 Gy, is one of the prerequisites for decreased tissue oxygenation. Consequently, energy production relies more on less efficient anaerobic mechanisms.

Analysis of the activity of key enzymes and the content of substrates involved in aerobic and anaerobic metabolism, as well as oxidative and substrate-level phosphorylation processes in the myocardium and skeletal muscle of the offspring of irradiated animals, revealed specific patterns. In the myocardium of offspring born to animals irradiated with 0.5 Gy and subsequently exposed to a dose of 1.0 Gy, a moderate decrease in pyruvate kinase activity was noted. The lowest value of this enzyme was recorded in the offspring whose parents were irradiated with 1.0 Gy and which themselves received the same dose; this value was almost 20% lower than in intact animals (Fig. 2).

The most pronounced changes were detected in skeletal muscles. In the offspring of animals irradiated with 0.5 Gy, which were additionally irradiated with 1.0 Gy, pyruvate kinase activity decreased insignificantly. In contrast, in 1-month-old rats born to animals irradiated with 1.0 Gy and re-irradiated with the same dose, this indicator was significantly lower compared to the control ($F(2, 27) = 3.464$; $p = 0.046$), measuring 238.2 nmol/mg protein per min of incubation.

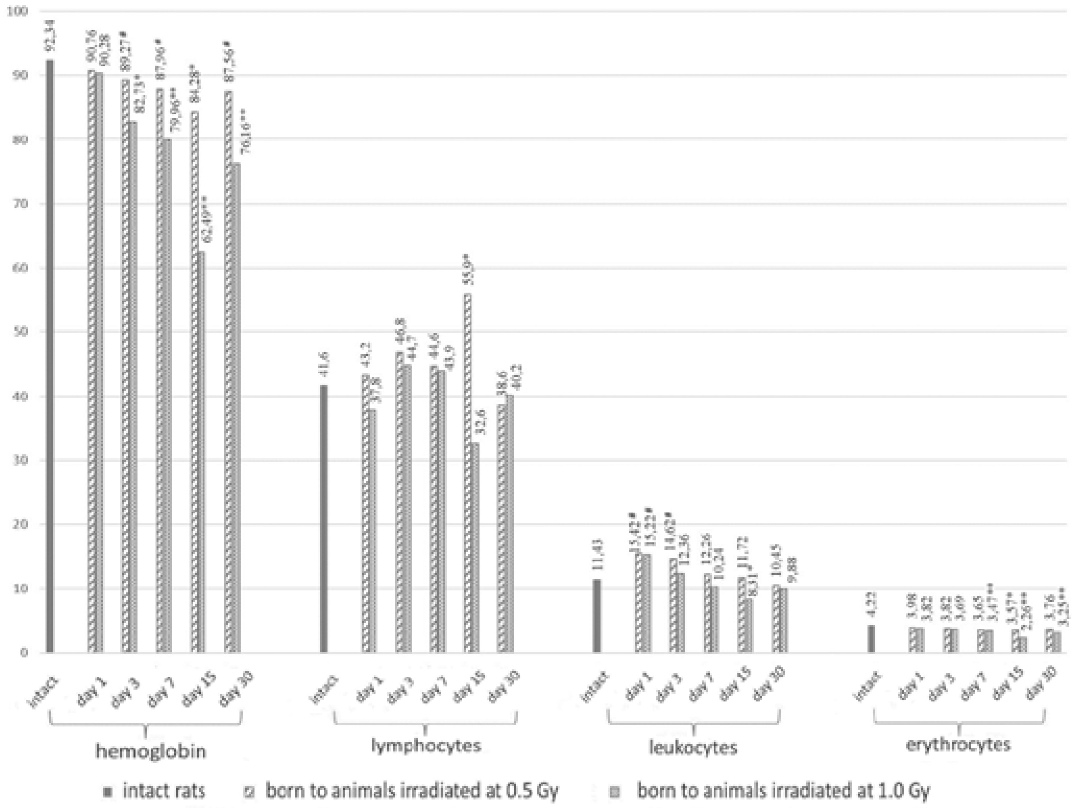

Fig. 1. Peripheral blood parameters of intact 1-month-old rats and 1-month-old rats born to animals irradiated at different doses and subjected to irradiation at a dose of 1.0 Gy (n = 10)

Notes:

1. Hemoglobin content is expressed in g/L, erythrocytes in 10^{12}/L, leukocytes in 10^9/L, lymphocytes in%.
2. # – p<0.05; * – p<0.01; ** – p<0.001 – significant differences compared to intact rats.

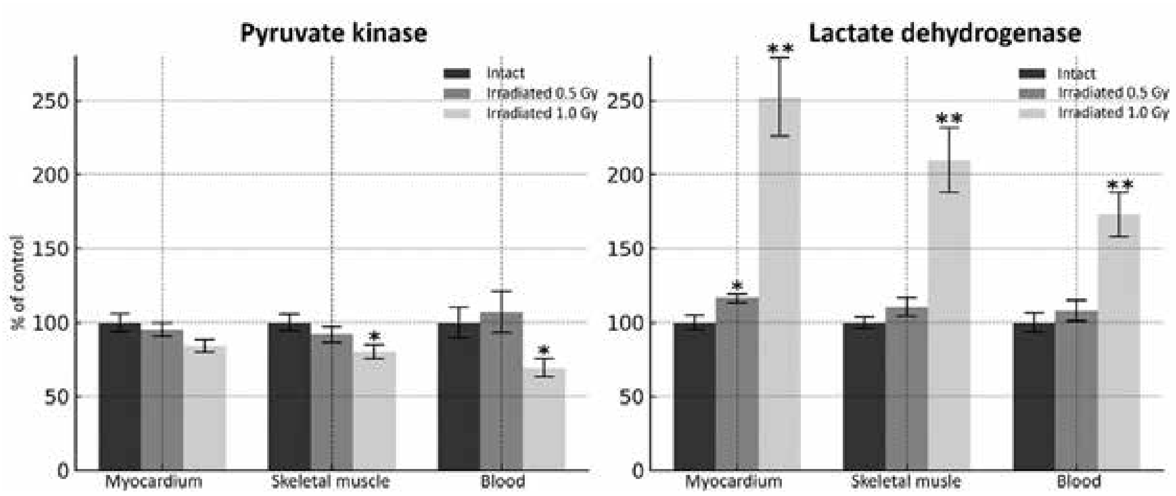

Fig. 2. Activity of pyruvate kinase and lactate dehydrogenase in muscle tissue and blood serum of intact 1-month-old rats and 1-month-old rats born to animals irradiated with different doses and subjected to irradiation at a dose of 1.0 Gy (n = 10)

Notes:

1. Pyruvate kinase activity in myocardium and skeletal muscles is expressed in nmol/mg protein per min; in blood serum, in nmol/mg protein per min.
2. Lactate dehydrogenase activity in myocardium and skeletal muscles is expressed in μmol/mg protein per min; in blood serum, in nmol/mg protein per min.
3. * – p < 0.05; ** – p < 0.001 – significant differences in the studied parameters compared to the corresponding parameters in intact animals.

Considering that glycolytic substrate-level phosphorylation is a primary energy source for skeletal muscles, these results indicate a reduced energy potential in this tissue, which inevitably affects the physical performance of offspring born to irradiated animals and subsequently exposed to the same radiation dose.

Pyruvate kinase activity in the blood of 1-month-old rats born to animals irradiated with a dose of 0.5 Gy and subsequently exposed to an additional 1.0 Gy dose was elevated compared to intact animals. In contrast, the blood of 1-month-old rats born to animals irradiated with a dose of 1.0 Gy and re-irradiated with the same dose showed a statistically significant decrease in enzyme activity ($F(2, 27) = 3.482$; $p = 0.045$), representing an approximately 1.5-fold reduction compared to intact animals.

The final stage of glycolytic metabolism is characterized by activation of lactate dehydrogenase (LDH). Increased LDH activity was noted both in peripheral blood and in all analyzed tissues of 1-month-old rats born to animals irradiated with 0.5 Gy and exposed to 1.0 Gy, compared to intact animals.

When the parental generation was irradiated with a dose of 1.0 Gy, a statistically significant increase in lactate dehydrogenase activity was observed in both the myocardium and skeletal muscles of their offspring, which were irradiated with the same dose. In the cardiac muscle cytoplasm of 1-month-old rats born to animals irradiated with 1.0 Gy and subsequently irradiated with the same dose, the enzyme activity increased by 2.5-fold ($H = 21.695$; $df = 2$; $p < 0.001$) compared to the intact control. In the skeletal muscle cytoplasm, this parameter exceeded control values 2.1-fold ($H = 16.312$; $df = 2$; $p < 0.001$), and in the blood serum, by 1.7-fold ($H = 13.169$; $df = 2$; $p < 0.001$).

The content of the products of the pyruvate kinase and lactate dehydrogenase reactions – pyruvate and lactate – was significantly higher in the studied tissues. The increase in these metabolites was dependent on the parental irradiation dose.

In the cardiac muscle of offspring born to animals irradiated with a dose of 0.5 Gy, the lactate concentration increased by 5.1% compared to control, whereas in offspring born to animals irradiated with 1.0 Gy, this indicator increased 1.64-fold ($H = 19.419$; $df = 2$; $p < 0.001$). Pyruvate levels increased by 9.6% in offspring of animals irradiated with 0.5 Gy and by 24.5% ($H = 6.939$; $df = 2$; $p < 0.01$) in offspring of animals irradiated with 1.0 Gy compared to intact animals. Consequently, the lactate/pyruvate ratio reached 11.52, which is 37.5% higher than the control (Fig. 3).

In the skeletal muscle of the offspring of animals irradiated with 0.5 Gy and subjected to irradiation at 1.0 Gy, the lactate level increased by 9.1%, while in the double-irradiated group it increased by 1.73 times ($H = 19.861$; $df = 2$; $p < 0.001$). Pyruvate increased by 4.9% and 15.3%, respectively, while the lactate/pyruvate ratio rose to 14.37, which is 1.44 times higher than the control.

In the blood of irradiated 1-month-old rats born to animals irradiated with 0.5 Gy, the lactate level increased by 22.7%, while in the offspring of animals irradiated with 1.0 Gy, this parameter was twice the control value ($H = 20.968$; $df = 2$; $p < 0.001$). Pyruvate concentration increased by 19.6% ($H = 16.547$; $df = 2$; $p < 0.05$) in the offspring of animals irradiated with 0.5 Gy and by 44.6% ($H = 16.547$; $df = 2$; $p < 0.001$) in offspring from animals irradiated with 1.0 Gy. The lactate/pyruvate ratio increased by 13.6% and 36.6%, respectively.

Thus, in the offspring born to irradiated animals and subsequently exposed to a 1.0 Gy dose, a significant accumulation of lactate is observed in the myocardium, skeletal muscle, and blood serum, accompanied by an increase in pyruvate levels and a rise in the lactate/pyruvate ratio. This indicates a shift in metabolism toward anaerobic glycolysis and activation of the lactate dehydrogenase pathway for energy supply.

The obtained data indicate that even during the early periods following irradiation, the offspring born to

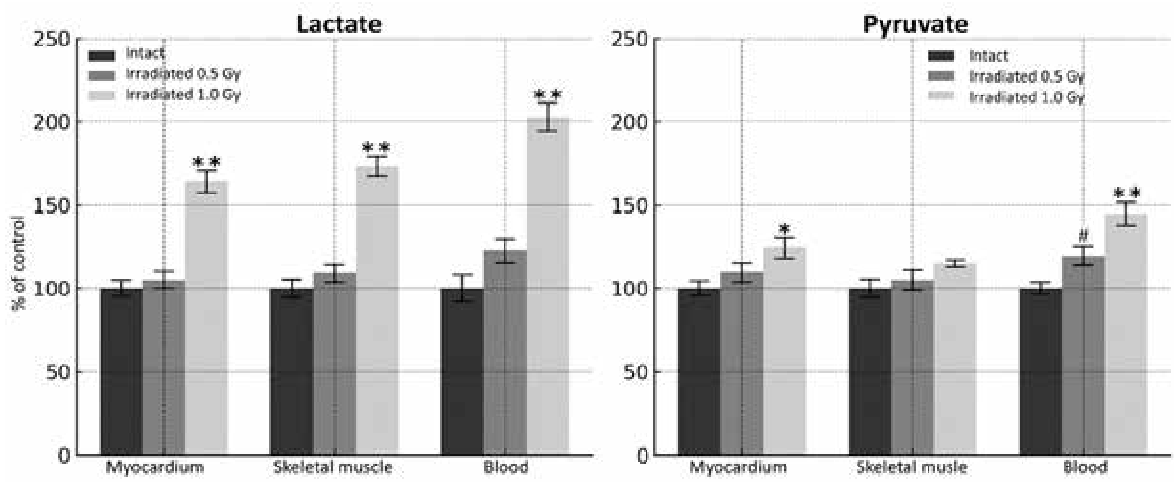

Fig. 3. Content of lactate and pyruvate in muscle tissue and blood serum of intact 1-month-old rats and 1-month-old rats born to animals irradiated at different doses and subjected to irradiation at a dose of 1.0 Gy (n = 10)

Notes:

1. Lactate and pyruvate content are expressed in µmol/g of tissue; in blood – in µmol/mL.
2. # – $p < 0.05$; * – $p < 0.01$; ** – $p < 0.001$ – significant differences compared to intact rats.

animals exposed to ionizing radiation develop pronounced alterations in peripheral blood parameters and energy metabolism. As early as one day after re-irradiation with a 1.0 Gy dose, a decrease in hemoglobin level and erythrocyte count was observed, alongside an increase in leukocyte, platelet, reticulocyte, and lymphocyte numbers. This suggests the activation of compensatory-adaptive processes in the hematopoietic system aimed at maintaining oxygen transport under conditions of radiation stress.

By days 3 and 7 post-irradiation, the changes intensified, manifesting as a significant decrease in hemoglobin and a trend towards suppression of erythropoiesis.

By day 15, the offspring of 0.5 and 1.0 Gy-irradiated animals exhibited minimal erythroid parameter values, accompanied by a significant reduction in hemoglobin concentration, erythrocytes, and platelets count. This indicates depletion of bone marrow reserves and a transition from the adaptive to the maladaptive phase of the hematological response. The partial restoration of the blood cell composition by day 30 points to the implementation of regenerative hematopoiesis mechanisms, although hemoglobin and erythrocyte levels remained below control values.

The decrease in hemoglobin and erythrocyte content in the peripheral blood could be a predisposing factor to tissue hypoxia, leading to a shift in energy metabolism towards less efficient anaerobic mechanisms. This is corroborated by the results of biochemical analysis, which indicate decreased pyruvate kinase activity and increased lactate dehydrogenase activity in the myocardium, skeletal muscles, and blood.

The observed decrease in pyruvate kinase activity in the skeletal muscles and blood of the offspring of 1.0 Gy-irradiated animals reflects the inhibition of the final stages of the glycolytic pathway and a reduction in the intensity of substrate-level phosphorylation. Conversely, the increase in lactate dehydrogenase activity and the elevated levels of lactate and pyruvate suggest a metabolic shift towards anaerobic glycolysis. The increased lactate/pyruvate ratio, particularly in skeletal muscles and blood, is indicative of the activation of the anaerobic energy-producing pathway, compensating for the ATP deficit under conditions of insufficient tissue oxygenation.

Thus, in the offspring of animals subjected to radiation exposure, a complex metabolic response develops, combining impaired erythropoiesis, reduced blood oxygenation capacity, and activation of anaerobic energy production aimed at maintaining cellular viability under hypoxic conditions.

Conclusions

1. In the offspring of animals irradiated with 0.5 or 1.0 Gy and subsequently re-exposed to 1.0 Gy, anemic changes appear as early as the first day after exposure. These are characterized by decreased hemoglobin levels and erythrocyte counts, accompanied by increased leukocyte and platelet numbers, indicating the activation of compensatory mechanisms within the hematopoietic system.

2. The most profound impairments in hematopoiesis are noted on the fifteenth day post-irradiation, when hemoglobin concentration and erythrocyte count reach their minimum values, suggesting suppression of bone marrow erythropoietic activity.

3. In the myocardium and skeletal muscles of the offspring born to irradiated animals, a decrease in pyruvate kinase activity and an increase in lactate dehydrogenase activity are observed. This is accompanied by an accumulation of lactate and pyruvate, an increased lactate/pyruvate ratio, and reflects a shift in energy metabolism towards anaerobic glycolysis. This shift leads to an energy deficit, which diminishes the adaptive and compensatory capabilities of the offspring of irradiated animals.

4. The obtained data indicate the formation of dose-dependent adaptive-maladaptive changes in the hematopoietic and energy supply systems in the offspring born to animals irradiated at different doses and subsequently exposed to an additional 1.0 Gy dose. This complex of changes could serve as an early biomarker of radiation exposure.

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Електронна адреса для листування alinakostina@ukr.net