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G.F. Stepanov, R.S. Vastyanov
Odesa National Medical University, Odesa

THE PECULIARITIES OF LOW-DOSE IONIZING RADIATION INFLUENCE ON MUSCLES METABOLISM IN EXPERIMENTAL ANIMALS

e-mail: medchem@ukr.net

The purpose of this study was to research the peculiarities of glycolytic processes manifestation in cardiac and striated muscles as a result of total irradiation exposure. 120 male rats were divided into 2 groups. Group 1 (n=20) – intact rats, group 2 (n=100) – rats that were exposed to ionizing gamma radiation. The animals were euthanized, blood was collected, the heart and the frontal group of thigh muscles were removed in which the pyruvate kinase and lactate dehydrogenase activities with its isozymes spectrum together with lactate and pyruvate content were measured. The pathophysiological mechanisms of radiation-induced energy supply reformation are aimed at strengthening of short-term processes of the energy supply to vital organs and systems for destroyed biochemical, physiological, functional and regulatory processes restitution and the sanogenetic mechanisms activation.

Key words: total irradiation, pyruvate kinase, lactate dehydrogenase, lactate, pyruvate, metabolism, pathophysiological mechanisms.

Г.Ф. Степанов, Р.С. Вастьянов

ОСОБЛИВОСТІ ВПЛИВУ МАЛИХ ДОЗ ІОНІЗУЮЧОГО ВИПРОМІНЮВАННЯ НА МЕТАБОЛІЗМ М'ЯЗІВ ЕКСПЕРИМЕНТАЛЬНИХ ТВАРИН

Метою дослідження було вивчення особливостей перебігу гліколітичних процесів у серцевому м'язі та поперечно-смугастих м'язах внаслідок впливу тотального опромінення. 120 щурів-самців були розділені на 2 групи. 1 група (n=20) – інтактні щури, 2 група (n=100) – щури, яких піддавали впливу іонізуючого гама-опромінення. Тварин виводили із дослідів через етаназії, збирали кров, видаляли серце і передню групу м'язів стегна, в яких вимірювали активність піруваткінази, лактатдегідрогенази з її ізоферментним спектром та вміст лактату і пірувату. Патолофізіологічні механізми спричиненої радіацією перебудови енергозабезпечення спрямовані на короточасні процеси посилення надання енергії для життєво важливих органів та систем задля відновлення зруйнованих біохімічних, фізіологічних, функціональних та регуляторних процесів та активацію саногенетичних механізмів.

Ключові слова: тотальне опромінення, піруваткіназа, лактатдегідрогеназа, лактат, піруват, метаболізм, патолофізіологічні механізми.

The study is a fragment of the research project "Mechanisms of epigenetic disorders of the leading links of bioenergetics and nitrogen metabolism in irradiated animals and their descendants", state registration No 0121U114601

In the current conditions of large-scale artificial radiation pollution of the environment and radiation load on the biosphere, the assessment of the total biological effectiveness of prolonged exposure is extremely relevant. The effect of radiation at a sufficiently high dose on biological objects in some cases is comparable to the effect of radiation at a dose ten times lower [13].

The radiation hazard of low-dose exposure has been shown to be significantly higher than that of maximum dose exposure. It should be emphasized that there is a pronounced alternative effect of acute and chronic low-dose radiation on the cellular genetic apparatus [11, 14].

Most of the results in the range of low doses of ionizing radiation indicate the existence of the effect of radiation hormesis, which is characterized by increased fertility, accelerated cell growth and

division, and increased life expectancy of biological objects [13–15]. Otherwise, radiation hormesis is understood as a set of phenomena with excess of vital functions, processes or physiological parameters as a result of exposure to ionizing radiation, i.e. as a hyperfunctional effect of ionizing radiation, rather than as an adverse effect of low doses of radiation.

Total irradiation of experimental animals at an average lethal dose causes significant changes in the cellular composition and protein composition of the blood, increases protein breakdown and mortality [8, 14]. It is also possible to register metabolic disorders in muscle tissue, which is known to be quite radioresistant. It is important that the nature of these disorders depends on the type of muscle [9, 13].

The mechanisms of ionizing radiation interaction with biological objects represents a chain of successive physical and physico-chemical changes which manifest themselves as excitation, primary and secondary ionization of molecules, which, in turn, leads to the appearance of excited atoms and free radicals which interact with each other as well as with intact biomolecules [7, 10]. We have noticed that the peculiarities of interaction of low doses of ionizing radiation with vital organs and systems have not been studied sufficiently, which allows us to perform a number of experimental studies on the pathophysiological mechanisms of reactions initiated in a biological organism in response to low doses of ionizing radiation. We are extremely interested in the details of the processes of energy supply of muscle activity in the body under the influence of ionizing radiation.

The purpose of the study was to establish the peculiarities of glycolytic processes manifestation in cardiac and striated muscles as a result of total irradiation exposure.

Materials and Methods. Experimental studies were performed on 120 white mature male Wistar rats. The animals were kept in standard vivarium conditions. The experimental animals were kept and manipulated in accordance with the “General Ethical Principles of Animal Experiments” adopted by the Fifth National Congress on Bioethics (Kyiv, 2013) and was guided by the recommendations of the European Convention for the Protection of Vertebrate Animals for Experimental and Other Scientific Purposes (Strasbourg, 1985) and guidelines of the State Pharmacological Center of the Ministry of Health of Ukraine on “Preclinical studies of drugs” (2001) as well as rules of humane treatment of experimental animals and conditions approved by the Committee on Bioethics of Odesa National Medical University (Prot. N32-D from 17.03.2016).

The animals were subjected to total gamma-irradiation of Co^{60} on an empty stomach using the “Agat” telegammatherapy unit. The absorbed dose was 6.0 Gr, and the radiation dose rate was 0.48 Gr/min. Rats lethality was equal to 43.0 % of irradiated animals (43 rats) in 1 month. The experimental animals were randomized into 2 groups: the 1st group (n=20) – intact rats, the 2nd group (n=100) – rats exposed to ionizing gamma-radiation (57 rats that survived during the 1-month study period).

The animals were euthanized by intravenous injection of propofol (60 mg/kg), after which the rats were dissected, blood was collected, and the heart and anterior thigh muscle group were removed. Blood was centrifuged at 3000 g for 10 min to obtain serum. Cardiac and skeletal muscle homogenates were prepared.

Mitochondria, mitochondrial supernatant of myocardium, frontal group of thigh muscles and blood serum were used for biochemical studies. Our attention was focused on pyruvate kinase (PK), lactate dehydrogenase (LDG) and its isozyme spectrum activity together with the lactate and pyruvate content. The tissues were immersed in liquid nitrogen followed by the addition of HCl to detect biosubstrates in the tissues [1].

The PK activity was determined according to its ability to convert phosphoenolpyruvate in the presence of ADP, then phosphoenolpyruvate turns into lactate in presence of reduced NAD and LDG, thereby oxidizing NADH [2]. Pyruvate kinase activity was expressed in pyruvate micromoles per mg of protein in the sample for 1 min of incubation. The LDG activity was determined according by pyruvate to lactate reduction in the presence of reduced NAD [1]. Lactate dehydrogenase activity was expressed in μ moles of $NADH^+$ per mg of protein in the sample for 1 min of incubation. Lactate dehydrogenase isozymes in tissues and blood were detected using polyacrylamide gel electrophoresis at a temperature of $+3^{\circ}C$ [1].

The content of lactate and pyruvate was determined enzymatically, the reaction is catalyzed by LDH in the presence of oxidized or reduced NAD. The obtained values are expressed in μ mol per 1 g of tissue [1].

The data obtained were calculated statistically using “T-tables” and χ^2 test. The minimum statistical probability was determined at $p < 0.05$.

Results of the study and their discussion. Table 1 presents data of pyruvate kinase activity in tissues and blood serum of animals after total gamma-irradiation.

The activity of PK which catalyzes the reaction of substrate phosphorylation and the synthesis of half of the ATP in glycolysis in myocardium of rats have increased on 1st day after irradiation ($p < 0.05$). The enzyme activity continued to increase on the 3rd and the 7th day of the trial and it reached the highest

value on the 7th day exceeding 1.3 times the same values in intact animals ($p<0.01$). On the 15th day of the trial – at the level of radiation sickness – one could register the significant drop of PK activity pertaining the same data throughout the previous period of the study, and it even became somewhat lower than in intact animals. Nothing changed until the end of the trial – on the 30th day of observation.

Table 1

Pyruvate kinase activity in tissues and blood serum of animals after total gamma-irradiation, (M±m)

N	Time after irradiation	Pyruvate kinase activity for 1 min of incubation		
		Myocardium, $\mu\text{mol}/\text{mg}$ protein	Skeletal muscles, $\mu\text{mol}/\text{mg}$ protein	Blood, nmol/mg protein
1	Intact, n=20	0.097±0.005	0.282±0.015	10.250±0.899
2	1 st day, n=11	0.112±0.003*	0.307±0.019	11.360±0.814
3	3 rd day, n=10	0.115±0.006*	0.324±0.019	11.750±1.147
4	7 days, n=10	0.126±0.006**	0.335±0.009**	12.040±1.846
5	15 days, n=15	0.085±0.003	0.227±0.013*	9.087±0.796
6	30 days, n=11	0.086±0.005	0.2367±0.024	9.486±1.472

Note: * – $p<0.05$ and ** – $p<0.01$ – the significant differences of the investigated indexes compared with the analogous data in control rats (χ^2 test).

The pattern of PK activity changes in skeletal muscles is identical to that occurring in the myocardium of irradiated animals. That demonstrates a gradual increase in enzyme activity until the 7th day after irradiation when its activity is more pertaining the same index in the control group by 19 % ($p<0.01$). Level of PK activity was going down until the 30th day a trial.

Principally the same pattern of PK activity for muscle tissue registered in blood – with wave-like index increase following by its decrease. Obtained data had insignificant changes compared with those in intact animals ($p>0.05$).

Table 2 presents data of lactate dehydrogenase activity in tissues and blood serum of animals after total gamma-irradiation.

Table 2

Lactate dehydrogenase activity in tissues and blood serum of animals after total gamma-irradiation, (M±m)

N	Time after irradiation	Lactate dehydrogenase activity for 1 min of incubation		
		Myocardium, $\mu\text{mol}/\text{mg}$ protein	Skeletal muscles, $\mu\text{mol}/\text{mg}$ protein	Blood, nmol/mg protein
1	Intact, n=20	1.542±0.076	2.060±0.094	8.118±0.545
2	1 st day, n=11	1.476±0.082	2.299±0.116	7.367±0.673
3	3 rd day, n=10	1.413±0.067	2.447±0.127*	7.160±0.677
4	7 days, n=10	1.824±0.063**	2.643±0.075**	9.175±0.549
5	15 days, n=15	1.967±0.096**	2.459±0.106**	10.550±0.748*
6	30 days, n=11	1.706±0.042	2.253±0.080	9.580±0.542

Note: * – $p<0.05$ and ** – $p<0.01$ – the significant differences of the investigated indexes compared with the analogous data in control rats (χ^2 test).

The LDG activity, which uses the product of the PK reaction as a substrate, in myocardium revealed slight increase on the 3rd day after irradiation, and its activity on the 7th day of the trial was equal to 1.824±0.063 $\mu\text{mol}/\text{mg}$ protein which is higher pertaining the same index in the control ($p<0.01$).

The 15th day showed the significant increase of this index compared to the intact rats ($p<0.01$). It should be noted that the activity of the enzyme did not differed significantly from intact animals ($p>0.05$).

The LDG activity in skeletal muscles was characterized by a gradual increase in activity starting from the 1st day. Its activity significantly prevailed the same data in the control observations throughout the 3rd till the 15 days of the trial ($p<0.05$).

The enzyme activity in blood serum showed the same trend of changes with significant increase on the 15th day after irradiation of the animals ($p<0.05$).

The revealed difference in LDG activity in muscles of irradiated animals accompanied by LDG isozymes composition difference in these tissues.

On the 1st day after irradiation, one could detect the LDG₁ and LDG₂ increase of the activity in myocardium ($p<0.05$), the LDG₃ and LDG₅ activity decreased twice ($p<0.01$) and the LDG₄ activity decreased by 5 times ($p<0.01$). On the 3rd day of the trial the LDG₁, LDG₂ and LDG₃ activity haven't changed ($p>0.05$) with the LDG₄ and LDG₅ activity simultaneous increased by 3 times and 2 times, correspondently (in both cases $p<0.01$), pertaining with the previous period of the study. On day 7 of the experiment, a significant decrease in LDH₁ activity ($p<0.05$) was observed with the restoration of LDH₃ activity and an increase in the activity of both LDH₄ and LDH₅ compared to the control ($p<0.05$). 15 days after irradiation of animals the LDG₁ and LDG₂ activity increased ($p<0.05$) together with decrease of both the LDG₃ and LDG₄

activities ($p < 0.05$). The same pattern of the LDG isozymes activity registered on the 30th day of the trial with one change – the LDG₁ activity was comparable with the same index in the control rats.

On the 1st day after the ionizing radiation the prevailed LDG₅ activity in skeletal muscles decreased due to the LDG₄ and LDG₃ activities increase ($p < 0.05$). On the 3rd day of the trial the LDG₅ activity decreased and the LDG₄ activity increased (in both cases $p < 0.05$) with the LDG₂ and LDG₃ normalized activities ($p > 0.05$). On the 7th day of the experiment one could observe the significant increase of LDG₅ activity ($p < 0.05$) with decreased activity of the remaining fractions of the enzyme ($p > 0.05$). The increased LDG₅ activity remained on the 15th and the 30th days of the trial while the other forms of the isozyme, especially LDG₁ and LDG₂, decreased ($p < 0.05$).

Fig. 1 presents the data on lactate content in the tissues of animals after total gamma-irradiation.

Lactate content in the muscle tissue and in the blood increases significantly on the 7th day of the trial until the end of observation exceeding the control values by 1.4–1.55 times ($p < 0.05$).

Content of pyruvate in tissues of animals after total gamma-irradiation is presented in Fig. 2.

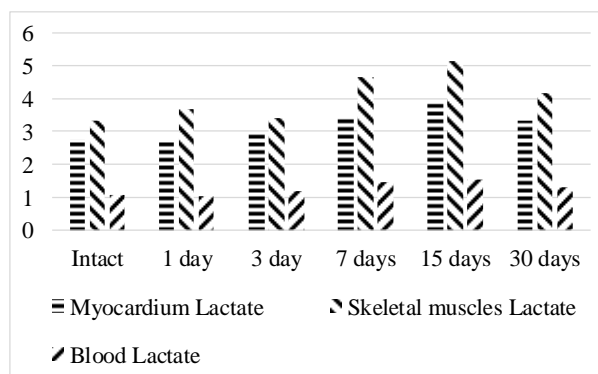


Fig. 1. Content of lactate in tissues of animals after total gamma-irradiation.

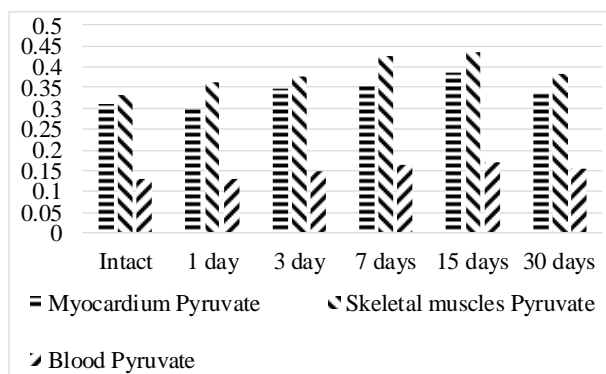


Fig. 2. Content of pyruvate in tissues of animals after total gamma-irradiation.

The concentration of pyruvate in the myocardium receives the significant difference from the control values on the 15th day of the trial where it prevails the same index in intact rats on 25.2 % ($p < 0.05$). By the end of the experiment, the content of pyruvate in the myocardium decreases and does not differ significantly from the control ($p > 0.05$).

The analogous picture is observed in skeletal muscles and blood where pyruvate activity significantly exceeds the control values on the 7th and the 15th days of the trial ($p < 0.05$) with its reestablishment on final day of the experiment ($p > 0.05$).

Thus, the data obtained indicate the expressed changes in the activity of the energy supply processes in skeletal and cardiac muscles of the biological organism in response to ionizing radiation medium-lethal doses influence. Among all the entire array of actual data, let us draw attention to three, in our opinion, main aspects.

First, the pattern of PC activity in skeletal muscle in response to ionizing radiation is identical to that in the myocardium of irradiated animals. It should be emphasized that the value of PC activity in skeletal muscle is lower than in myocardium. The likely explanation for this fact is that, unlike the heart muscle, glycolysis is the leading energy source in skeletal muscle, and therefore a decrease in the activity of substrate phosphorylation processes leads to a decrease in the functional capacity of skeletal muscle.

Secondly, what seems to be important regarding the activity of LDH. We noted that the activity of this enzyme in the heart muscle was characterized by an initial slight decrease on day 3 of the study, followed by periods of gradual increase, reaching the highest values on day 15. On the contrary, LDH activity in skeletal muscle showed an increase from the first day with a peak of activity on day 7, after which a gradual normalization of the enzyme function in this tissue was observed.

Thirdly. Interestingly, the spectrum of LDH isozymes in the studied muscles is characterized by a decrease in LDH₁ activity and an increase in LDH₅ activity at the height of the modeled pathological condition, which is quite characteristic of hypoxia and increased anaerobic processes. In addition, despite the general normalization of LDH activity in the tissues of irradiated animals at the end of the experiment, the spectrum of LDH isozymes remains sharply altered, indicating the depth of the changes that occur and do not disappear even 30 days after irradiation. It is noteworthy that the maximum activity of LDH after irradiation in both cardiac and skeletal muscles is accompanied by the maximum content of its isozymes present in each tissue.

Critically analyzing the actual data, we emphasize that they are in a certain relationship with the results of a number of scientific papers that prove both adaptive and compensatory restructuring of organisms under the influence of low doses of ionizing radiation [3–5, 11]. In this regard, we consider it necessary to emphasize the following:

The lactate/pyruvate ratio throughout the experiment demonstrates dynamics from unchanged to increased values compared to control animals, which is due to the fact that the accumulation of lactate in the studied tissues outpaces the increase in pyruvate concentration during the same period. We assume that the increase in pyruvate content within 3–15 days after irradiation is associated with the initiation of the pyruvate kinase reaction and the accumulation of its metabolites within 1–7 days, as well as with the destruction of muscle tissue and protein breakdown, as well as an increase in amino acid deamination [6, 7].

An increase in the number of migrating LDH isozymes in tissues at the height of the disease was accompanied by an increase in both the amount of lactate and the lactate/pyruvate ratio, indicating an increase in anaerobic processes. Assuming that the lactate/pyruvate ratio is similar to the NADPH/NAD ratio, the increase in lactate/pyruvate indicates the restoration of the activity of nicotinamide coenzymes within 7–30 days of the experiment. Since reduced nicotinamide coenzymes are inhibitors of pyruvate kinase [7] and LDH activity depends not so much on the absolute concentration of the coenzyme as on the ratio of its oxidized and reduced forms [7, 12], it is understandable that the decrease in PC activity at the peak of ionized radiation and, as a result, the decrease in phosphorylation of tissue substrates along with the increase in LDH activity in the pyruvate-lactate direction, when the reduced form of the coenzyme is involved in the reaction, is understandable. To test this assumption, we investigated the activity of LDH in the conversion of lactate to pyruvate at different periods of radiation sickness. We found that while the enzyme increases its activity in the direction of pyruvate to lactate reduction, its ability to catalyze the oxidation of lactate to pyruvate decreases, leading to significant accumulation of lactate in the tissues. Thus, total gamma-irradiation of experimental animals at mid-lethal doses causes an increase in the phosphorylation of glycolytic substrates in the initial and latent periods of radiation sickness in the blood, as well as in skeletal and cardiac muscles. The intensity of this process decreases in the midst of the disease, the activity of LDH in muscle tissue increases, the spectrum of its isozymes is characterized by an increase in the content of slowly migrating isozymes, accompanied by an increase in the content of metabolites of both lactate and pyruvate reactions, as well as an increase in the lactate/pyruvate ratio. We expect that the pathophysiological mechanisms of radiation-induced restructuring of energy supply are aimed at enhancing short-term energy supply processes of vital organs and systems to restore disturbed biochemical, physiological, functional and regulatory processes and activate sanogenetic mechanisms.

Conclusions

1. The experimental animal's total gamma irradiation in medium-lethal doses causes a glycolytic substrate phosphorylation increase during the initial and hidden periods of radiation sickness in blood along with skeletal and cardiac muscles.

2. The pathophysiological mechanisms of radiation-induced energy supply reformation are aimed at strengthening short-term processes of the energy supply to vital organs and systems for destroyed biochemical, physiological, functional and regulatory processes restitution and the sanogenetic mechanisms activation.

Prospects for further research include a further search of the peculiarities of muscle tissue energy supply processes in the descendants of irradiated animals with the aim of comparative evaluation of the efficiency of stimulated energy supply mechanisms in response to small doses of radiation exposure that are involved into the ready genetic program.

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**Yu.V. Tymoshenko, G.A. Yeroshenko, O.V. Kulai, O.B. Ryabushko, K.V. Shevchenko,
N.A. Ulanovska-Tsyba, L.V. Stotska
Poltava State Medical University, Poltava**

METHACRYLIC ACID ETHER-RELATED CHANGES IN THE INTENSITY OF MARKING OF COMPONENTS OF THE RAT HARD PALATE MUCOSA REVEALED BY PROBING WITH SIALO-SPECIFIC SNA LECTIN FROM THE BARK OF *SAMBUCUS NIGRA*

The decrease in secretory activity of the salivary glands disrupts local homeostasis in the oral cavity, affects the functioning of the entire digestive system, inhibits processes of physiological regeneration and impairs the protective properties of the mucous membrane against antigens. We have found changes in the morphofunctional state of the hard palate mucosa during the experimental hyposalivation using lectin probing method.

Key words: hyposalivation, hard palate mucosa, methacrylic acid ether, elderberry bark lectin.

**Ю.В. Тимошенко, Г.А. Єрошенко, О.В. Кулай, О.Б. Рябушко, К.В. Шевченко,
Н.А. Улановська-Циба, Л.В. Стоцька**

ЗМІНИ ІНТЕНСИВНОСТІ МАРКУВАННЯ КОМПОНЕНТІВ СЛИЗОВОЇ ОБОЛОНКИ ТВЕРДОГО ПІДНЕБІННЯ ЩУРІВ ПРИ ЗОНДУВАННІ СІАЛОСПЕЦИФІЧНИМ ЛЕКТИНОМ КОРИ БУЗИНИ ЧОРНОЇ (SNA) ТА ПІСЛЯ ДІЇ ЕФІРУ МЕТАКРИЛОВОЇ КИСЛОТИ

Зниження секреторної активності слинних залоз порушує місцевий гомеостаз в ротовій порожнині, відображається на роботі всієї системи травлення, гальмує процеси фізіологічної регенерації та порушує захисні властивості слизової оболонки до антигенів. Нами були визначені зміни морфофункціонального стану слизової оболонки твердого піднебіння за умов експериментальної гіпосалівації методом лектинового зондування.

Ключові слова: гіпосалівація, слизова оболонка твердого піднебіння, ефір метакрилової кислоти, лектин кори бузини чорної.

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The secretory activity of the salivary glands plays a crucial role in maintaining oral microbial balance and homeostasis. Decreased salivary secretion is exacerbated in concomitant somatic pathologies, use of medications and wearing of removable dentures [3, 5]. This affects both the local manifestations of dental pathology and the overall human somatic health.

The functions of maintaining the integrity of the oral tissues are primarily performed by unstimulated (at rest) salivary secretion. Salivary functions related to digestion are performed by stimulated saliva [4], which plays a particularly important role in conditions associated with decreased saliva production, also known as hyposalivation [2, 12]. At this point, patients with hyposalivation experience constant dryness in the oral cavity, called xerostomia, which leads to the rapid onset of inflammatory processes and the active progression of dental caries [5, 11]. Aggregations of leukocytes, which provide a physiological barrier against infection [1, 7, 8, 15], are localized in the connective tissue of the mucous membrane, which serves as the stroma for the minor salivary glands, and this barrier is disrupted when secretion is reduced. Hyposalivation not only disrupts local homeostasis in the oral cavity but also affects