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INVOLVEMENT OF INTRAMUSCULAR PATHOLOGY AT THE LEVEL OF THE ACTOMYOSIN JUNCTION INTO THE PATHOGENETIC MECHANISMS OF MUSCLE DYSFUNCTIONSIN THE DESCENDENTS OF IRRADIATED RATS

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The purpose of the study was to assess the contractile proteins concentration and the dynamics of ATP-ase activity changes in striated and cardiac muscles of irradiated animals descendents. 130 1-month-old rats were divided into 3 groups in accordance to the dose of ionizing radiation given to them and theirs parents. The heart and the frontal group of thigh muscles were removed in which the contractile muscle proteins concentration and the muscle ATP-ase activity were determined. The ionizing radiation influence causes a disturbance in skeletal and cardiac muscles functioning in irradiated animals' descendents manifested by muscle structure structural unit dysfunction – the actomyosin junction and muscle contraction energy supply disturbance realized by ATP-ase enzymatic system activity significant decrease. A more alterative effect of ionizing radiation on the cardiac muscle has been proven. The authors proved that leading links in the body and the muscle system radiation damage pathogenesis are the muscles functional state dysfunction, metabolic resources degradation, biochemical processes inversion, depletion of the energy supply of the muscle contractile function and the contractile intramuscular apparatus disruption. The core mechanism for radiation-induced muscle dysfunctions pathogenetically oriented scheme of pharmacological correction realization should be radioprotective and muscle-protective efficacy which will provide the opportunity to restore destroyed biochemical, physiological, electrical, functional and regulatory processes and activate sanogenetic mechanisms.

Key words: ionizing irradiation, descendents of irradiated animals, actin, myosin, troponin tropomyosin, ATPase activity, pathophysiological mechanisms

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ЗАЛУЧЕННЯ ВНУТРІШНЬОМ'ЯЗОВОЇ ПАТОЛОГІЇ НА РІВНІ АКТО-МІОЗИНОВОГО З'ЄДНАННЯ ДО ПАТОГЕНЕТИЧНИХ МЕХАНІЗМІВ М'ЯЗОВИХ ДИСФУНКЦІЙ У НАЩАДКІВ ОПРОМІНЕНИХ ЩУРІВ

Метою роботи було дослідження концентрації скорочувальних білків та динаміки змін АТФ-азної активності у поперечно-смугастих м'язах та серцевому м'язі нащадків опромінених у різних дозах тварин. 130 щурів віком 1 місяць було розділено 3 групи відповідно дози іонізуючого опромінення, отриманої ними та їхніми батьками. В щурів видаляли серце і передню групу м'язів стегна, в яких визначали концентрацію скоротливих м'язових білків і м'язову АТФ-азну активність. Вплив іонізуючого опромінення спричиняє порушення функціонування скелетного та серцевого м'язів у нащадків опромінених тварин, що проявляється дисфункцією структурної одиниці будови м'язів – акто-міозинового з'єднання та порушення енергетичного забезпечення м'язового скорочення, реалізоване суттєвим зменшенням активності АТФ-азної ферментативної системи. Доведено більш альтеративний вплив іонізуючого опромінення на серцевий м'яз. Автори довели, що провідними ланками патогенезу радіаційного ураження організму та м'язової системи є порушення функціонального стану м'язів, деградація метаболічних ресурсів, інверсія біохімічних процесів, виснаження енергетичного забезпечення скоротливої функції м'язів та порушення функціонування скоротливого апарату м'язів. Провідним механізмом реалізації антирадіаційного впливу патогенетично обґрунтованої схеми фармакологічної корекції спричинених радіацією м'язових дисфункцій має бути радіопротекторна та м'язовозазисна ефективність, що надасть можливість відновлення зруйнованих біохімічних, фізіологічних, електричних, функціональних та регуляторних процесів та активацію саногенетичних механізмів.

Ключові слова: іонізуюче опромінення, нащадки опромінених тварин, актин, міозин, тропонін, тропоміозин, АТФ-азна активність, патофізіологічні механізми

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The interest of specialists in the effects of ionizing radiation is determined by the scope of its practical use for the needs of mankind. The widespread use of ionizing radiation in the field of nuclear energy, cases of large-scale industrial accidents at nuclear facilities and military nuclear installations as well as the progressive nature of nuclear weapons use including military weapons with depleted uranium – these reasons require a thorough study of ionizing radiation influence on biological organism [1, 2]. The accumulated experience allows to assess the nature of radiation-induced damage to the human body, the extent of systemic damage depending on the radiation dose and to correct radiation-induced functional disorders [8, 13].

After ionizing radiation interferes with biological organism the latter absorbs radiation energy which results in atoms and molecules ionization or excitation. Ions and free electrons formed as a result of atoms ionization interact with each other and with the intact surrounding atoms and molecules, forming free radicals [1]. Additionally, ionizing radiation breaks covalent bonds contributing to free radicals' formation and changing the polymer chains and macromolecule's structure [6].

Under the influence of ionizing radiation and free radicals, the molecules of the cellular main biologically important organic substances – DNA, nucleotides, amino acids, proteins, carbohydrates, phospholipids, etc. – undergo radiolysis with the organic radical's formation that provide an alterative impact on the tissue [10]. As the result, hyperactive free radicals, products of water radiolysis, active forms of oxygen and organic radicals are capable to change the biologically important macromolecule's structure and disrupt their function. The processes taking place in proteins, DNA and phospholipids have the greatest importance for the further fate of the irradiated cell [6].

The muscle system is proved to be one of the structural systems of the human body that receives the first impact of ionizing radiation. It was found that radiation-induced numerous structural and functional changes in subcellular structures lead to oxidative phosphorylation processes disturbances which leads to cellular energy resources depletion, lysosomal hydrolytic enzymes release and activation, DNA synthesis and cell division suppression, ion transport perversion, etc [11]. One should remember about the hepatic macrophages that play a leading role in internal organ homeostasis maintaining and in the pathogenesis of its damage [12]. The muscle cells metabolism disturbance is the results of the named chain of pathological processes manifestation, one could believe that the nature muscle dysfunction determines by the type of muscles [10, 14, 15].

The number of people suffered by the different source of ionizing radiation has grown rapidly over the past decade [1]. The current military aggression against Ukraine increases the urgency of this medical and biological problem. Unfortunately, we have not received fundamental knowledge about the pathogenetic mechanisms of radiation-induced muscles dysfunctions. This concern, especially, the most important muscle fibers contractile element – the actin-myosin complex [11]. This becomes the subject of our attention, since it is the actin-myosin interaction becomes the basis of muscle tissue contraction [7, 11]. These two proteins have the ability to split ATP molecules, thereby releasing the energy needed to ensure muscle contraction. It is interesting that ATP-ase activity is also the actomyosin characteristic – the main component of the muscle contractile apparatus which, additionally to its structural and contractile function, provides enzymatic Ca^{2+}-dependent Mg^{2+}-regulated cleavage of ATP. ADP release as a result of ATP-ase reaction has the limiting effect of the actin-myosin interaction [7].

One could understand our efforts to investigate the pathogenetic mechanisms of muscle disorders in irradiated peoples descendants after ionizing radiation impact if we recall the age of people exposed to Chernobyl disaster ionizing radiation.

The purpose of the study was to assess the contractile proteins concentration and the dynamics of ATP-ase activity changes in striated and cardiac muscles of irradiated animals descendents.

Materials and methods. Experimental studies were performed on 120 white matured and 130 1-month-old Wistar rats. The animals were kept in standard vivarium conditions. Experimental animals keeping and manipulation was done 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, the radiation dose rate was 0.48 Gr/min. Rats lethality was equal to 43.0% of irradiated animals (43 rats) in 1 month. Experimental animals initially were randomized on 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). Further, 57 sexually mature white Wistar rats were used in the study, and parents were set in the ratio of 1 male to 5 females. The irradiated animals' descendents were not separated by sex.

1-month-old rat pups after irradiation were randomized into the following groups: the 1st group (n=10) – 1-month-old rat pups born from intact animals; the 2nd group (n=60) – 1-month-old rat pups born from once irradiated animals with a dose of 0.5 Gy and exposed to radiation with a dose of 0.5 Gy; the 3rd group (n=60) – 1-month-old rat pups born from once irradiated animals with a dose of 1.0 Gy and exposed to radiation with a dose of 1.0 Gy.

Rat pups of the 2nd and the 3rd groups were euthanized by i.v. propofol (60 mg/kg) injections 1 hr, 1, 3, 7, 15 and 30 days after irradiation in the amount of 10 animals per each set of investigation. The frontal group of thigh muscles and heart were removed after the rats were dissected.

To determine the myosin concentration, muscle tissue was crushed and ground during 10 min at a temperature of 4 ^{0}C in a ratio of 1:10 in a solution containing 20 mM phosphate buffer, 4 mM $MgCl_2$, 1 mM

EGTA, 2% Triton X-100, 5 mM dithiothreitol, 0.5 mM of phenylmethylsulfonyl fluoride, pH=6.5. The further technology for myosin obtaining which was prepared and used separately in each day of the trial complied with generally accepted methods [4].

Actin, troponin and tropomyosin were isolated from acetone powder according to generally accepted method with minor modifications [4] All these operations were performed at a temperature of 4 ºC. The purity of contractile proteins was assessed using denaturing polyacrylamide gel electrophoresis with sodium dodecyl sulfate in 10 % solution according to Laemmli method [4]. Contractile proteins content is expressed in μmol per 1g of tissue.

Both actomyosin and myosin ATPase activity was determined by the amount of inorganic phosphate (P*i*) formed as a result of ATP hydrolysis, according to the Fiske-Subbarow method [4].

The ATPase reaction was initiated by 0.2 ml of 1 mM ATP adding to the incubation space and expressed in nmol P*i*/min per 1 mg of protein. The reaction was stopped 5 min after by adding 0.45 ml of 20 % trichloroacetic acid to the sample (the final content in the sample was 4 %). After that, the samples were centrifuged at 2500 rpm during 15 min and 1.5 ml of supernatant was removed from each test tube to determine the amount of separated P*i* in it using the characteristic color.

The data obtained were calculated statistically using "T-tables" and $\chi 2$ test. The minimum statistical probability was determined at $p<0.05$.

Results of the study and their discussion. The contractile proteins content in the skeletal and cardiac muscles of descendents born from animals once irradiated at a dose of 0.5 Gy is insignificantly higher compared with the same values in intact rat pups (Table 1).

Table 1

The content of contractile proteins in skeletal and cardiac muscles of animals' descendants once irradiated at different doses and later exposed to 1.0 Gy radiation

Investigated indices	Investigated tissues	Control	Before irradiation	After irradiation				
				Day 1	Day 3	Day 7	Day 15	Day 30
Parents irradiated by 0.5 Gy, descendents irradiated by 1.0 Gy								
Myosin	Skeletal muscle	4.86±2.58	5.42±2.62	4.28±2.46	3.62±2.34	2.88±2.26*#	3.14±2.28	3.84±2.36
	Cardiac muscle	5.24±2.68	6.16±2.72	5.12±2.54	4.78±2.42	4.08±2.26	4.52±2.46	4.98±2.54
Actin	Skeletal muscle	1.98±0.26	2.16±0.28	1.34±0.22	1.04±0.18*#	0.86±0.14*#	0.98±0.16*#	1.16±0.18*#
	Cardiac muscle	2.76±0.32	2.96±0.36	2.34±0.28	2.12±0.24	1.76±0.22*#	2.36±0.28	2.64±0.32
Troponin	Skeletal muscle	0.88±0.12	0.96±0.14	0.42±0.12*#	0.26±0.08*#	0.16±0.04*#	0.22±0.06*#	0.32±0.08*#
	Cardiac muscle	0.96±0.16	1.18±0.21	0.92±0.16	0.64±0.14*#	0.42±0.12*#	0.84±0.16	0.90±0.18
Tropomyosin	Skeletal muscle	0.98±0.14	1.12±0.18	0.54±0.12*#	0.32±0.08*#	0.21±0.04*#	0.32±0.06*#	0.46±0.08*#
	Cardiac muscle	1.02±0.18	1.34±0.22	1.02±0.18	0.86±0.16	0.54±0.14*#	0.92±0.16	0.98±0.18
Parents irradiated by 1.0 Gy, descendents irradiated by 1.0 Gy								
Myosin	Skeletal muscle	4.86±2.58	3.42±2.24	3.12±2.22	2.86±2.26	2.62±1.88	2.28±1.84	1.98±1.26
	Cardiac muscle	5.24±2.68	4.74±2.32	4.36±2.24	3.94±2.1	3.48±2.14	3.16±1.98	2.88±1.76
Actin	Skeletal muscle	1.98±0.26	1.24±0.22	1.12±0.18	0.82±0.1*	0.68±0.14*	0.46±0.1*#	0.22±0.08*#
	Cardiac muscle	2.76±0.32	2.26±0.24	2.12±0.22	2.04±0.1	1.98±0.16	1.54±0.1*	1.22±0.12*#
Troponin	Skeletal muscle	0.88±0.12	0.62±0.11	0.44±0.08*	0.34±0.0*	0.21±0.04*#	0.16±0.0*#	0.12±0.02*#
	Cardiac muscle	0.96±0.16	0.72±0.14	0.56±0.12	0.42±0.0*	0.34±0.06*#	0.22±0.0*#	0.14±0.02*#
Tropomyosin	Skeletal muscle	0.98±0.14	0.54±0.12*	0.38±0.08*	0.32±0.0*	0.24±0.04*	0.18±0.0*#	0.14±0.02*#
	Cardiac muscle	1.02±0.18	0.69±0.16	0.48±0.12*	0.32±0.0*	0.26±0.04*#	0.18±0.0*#	0.12±0.02*#

Note: * – $p<0.05$ – the significant differences of the investigated indexes compared with the analogous data in control rats ($\chi 2$ test). # – $p<0.05$ – the significant differences of the investigated indexes compared with the analogous data in rats' pups before irradiation ($\chi 2$ test).

1 day after descendents irradiation by 1.0 Gy born from parents once irradiated at a dose of 0.5 Gy (the 2nd group) troponin and tropomyosin concentration in skeletal muscle was equal to 0.42±0.12 μmol/g and 0.54±0.12 μmol/g, respectively, which was in 2.1 times less and 1.8 times less compared to such indexes in control rats. These data were also 2.3 times and 2.1 times less, respectively, pertaining such indexes before irradiation ($p<0.05$). The rest of investigated indexes in this term were comparable to same values before irradiation ($p>0.05$).

With the time after irradiation, the contractile proteins concentrations decreased in skeletal and cardiac muscles compared the same values in control observations and in rats before irradiation. The maximal decrease was set 7 days after irradiation where the myosin content in skeletal muscle was less by 41 , the actin content was less by 2.3 times, troponin and tropomyosin concentrations were by 5.5 times and by 4.7 times less pertaining the same indexes in control rats and in pups before irradiation ($p<0.05$).

In cardiac muscle, the content of actin was 1.6 times less, troponin – 2.3 times and tropomyosin – 1.9 times less compared to corresponding values in intact rats and in pups before irradiation (in all cases $p<0.05$). Myosin concentration reveals less by 22% which was comparable with intact rats indexes ($p>0.05$).

An increase in contractile proteins levels in skeletal and cardiac muscles was observed later, on the 15th and the 30th days of the trial. Actin, troponin and tropomyosin concentrations in skeletal muscle in these days were significantly lower compared with such indexes before irradiation ($p<0.05$). The value of investigated parameters in the cardiac muscle during these trial periods did not differ from the similar data in rat pups before irradiation ($p>0.05$).

1 day after descendents irradiation by 1.0 Gy born from parents once irradiated at a dose of 1.5 Gy (the 3rd group) troponin concentration in skeletal and cardiac muscles as well as tropomyosin level in skeletal muscle were significantly less compared with corresponding control indicators ($p<0.05$).

Contractile muscle proteins concentration in the following time intervals and until the end of the observation decreased in skeletal and cardiac muscles compared with such indexes in intact animals and rats' pups before irradiation. The investigated values were minimal on the 30th day after irradiation where the myosin content in skeletal muscle was by 2.5 times less ($p>0.05$), the actin concentration – by 9 times less, troponin level – by 7.3 times and tropomyosin – by 7 times less compared with the same indexes in intact animals and rats' pups before irradiation (in all cases $p<0.05$).

The actin level in the cardiac muscle was 2.3 times less, troponin – 6.8 times and tropomyosin – 8.5 times less pertaining the corresponding values in intact animals and rats' pups before irradiation (in all cases $p<0.05$).

Mg^{2+}, Ca^{2+}-ATPase- and K^{+}-ATPase activity of actomyosin during the entire observation period after irradiation in rats of the 2nd group did not differ from the corresponding control indexes and data in rats' pups before irradiation ($p>0.05$; Table 2).

Mg^{2+}, Ca^{2+}-ATPase activity of myosin in skeletal muscle was less than comparing the same indexes in control observations and in rats before irradiation starting from the 7th day after irradiation and till the end of the trial ($p<0,05$).

K^{+}-ATP-ase activity of myosin in the cardiac muscle in rats of this group was significantly reduced in relation to the control indexes and the corresponding values before irradiation starting from the 15th day after irradiation ($p<0.05$).

Muscle tissue ATPase activity in rats born from animals once irradiated by 1.0 Gy which were exposed to irradiation at the same dose (the 3rd group) underwent more profound changes. In the descendents of animals irradiated at a dose of 1.0 Gy, Mg^{2+}, Ca^{2+}-ATP-ase activity of actomyosin ($p>0.05$) and myosin ($p<0.05$) and K^{+}-ATP-ase activity of actomyosin ($p>0.05$) and myosin ($p<0.05$) in skeletal and cardiac muscles were lower compared to same indexes in intact animals.

Rat pups born from animals once irradiated by 1.0 Gy after irradiation at a dose of 1.0 Gy demonstrated both Mg^{2+}, Ca^{2+}-ATP-ase and K^{+}-ATP-ase activity of actomyosin and myosin in all types of muscles decrease with the time increasing after irradiation. The lowest values were obtained on the 30th day of the trial.

Mg^{2+}, Ca^{2+}-ATP-ase activity of actomyosin and myosin in skeletal muscle was in 2.2 times and 2.8 times, respectively, less compared with the same values in intact animals ($p<0.05$). K^{+}-ATP-ase activity of actomyosin and myosin in skeletal muscle was in 1.6 times and 2 times, respectively, less pertaining the same control indexes ($p<0.05$). All these data were significantly less vs the same indexes before irradiation ($p<0.05$).

K^+-ATP-ase activity of myosin in cardiac muscle on the 30th day after irradiation was 1.5 times less compared to same index in intact animals. Mg^{2+}, Ca^{2+}-ATP-ase activity of actomyosin and myosin in cardiac muscle was in 1.8 timed and in 2.1 times, respectively less pertaining the same control values ($p<0.05$). All listed indexes were significantly less comparing with the same values before irradiation ($p<0.05$).

Table 2

ATP-ase activity of actomyosin and myosin in skeletal and cardiac muscles of animals' descendents once irradiated at different doses and later exposed to 1.0 Gy radiation

Investigated indices	Investigated tissues	Control	Before irradiation	After irradiation				
				Day 1	Day 3	Day 7	Day 15	Day 30
Parents irradiated by 0.5 Gy, descendents irradiated by 1.0 Gy								
Myosin	Skeletal muscle	4.86±2.58	5.42±2.62	4.28±2.46	3.62±2.34	2.88±2.26*#	3.14±2.28	3.84±2.36
	Cardiac muscle	5.24±2.68	6.16±2.72	5.12±2.54	4.78±2.42	4.08±2.26	4.52±2.46	4.98±2.54
Actin	Skeletal muscle	1.98±0.26	2.16±0.28	1.34±0.22	1.04±0.18*#	0.86±0.1*#	0.98±0.16*#	1.16±0.18*#
	Cardiac muscle	2.76±0.32	2.96±0.36	2.34±0.28	2.12±0.24	1.76±0.22*#	2.36±0.28	2.64±0.32
Troponin	Skeletal muscle	0.88±0.12	0.96±0.14	0.42±0.12*#	0.26±0.08*#	0.16±0.04*#	0.22±0.06*	0.32±0.08*#
	Cardiac muscle	0.96±0.16	1.18±0.21	0.92±0.16	0.64±0.14*#	0.42±0.12*#	0.84±0.16	0.90±0.18
Tropomyosin	Skeletal muscle	0.98±0.14	1.12±0.18	0.54±0.12*#	0.32±0.08*#	0.21±0.04*#	0.32±0.06*#	0.46±0.08*#
	Cardiac muscle	1.02±0.18	1.34±0.22	1.02±0.18	0.86±0.16	0.54±0.14*#	0.92±0.16	0.98±0.18
Parents irradiated by 1.0 Gy, descendents irradiated by 1.0 Gy								
Myosin	Skeletal muscle	4.86±2.58	3.42±2.24	3.12±2.22	2.86±2.26	2.62±1.88	2.28±1.84	1.98±1.26
	Cardiac muscle	5.24±2.68	4.74±2.32	4.36±2.24	3.94±2.16	3.48±2.14	3.16±1.98	2.88±1.76
Actin	Skeletal muscle	1.98±0.26	1.24±0.22	1.12±0.18	0.82±0.16*	0.68±0.14*	0.46±0.12*#	0.22±0.08*#
	Cardiac muscle	2.76±0.32	2.26±0.24	2.12±0.22	2.04±0.18	1.98±0.16	1.54±0.14*	1.22±0.12*#
Troponin	Skeletal muscle	0.88±0.12	0.62±0.11	0.44±0.08*	0.34±0.06*	0.21±0.04*#	0.16±0.04*#	0.12±0.02*#
	Cardiac muscle	0.96±0.16	0.72±0.14	0.56±0.12	0.42±0.08*	0.34±0.06*#	0.22±0.04*#	0.14±0.02*#
Tropomyosin	Skeletal muscle	0.98±0.14	0.54±0.12*	0.38±0.08*	0.32±0.06*	0.24±0.04*	0.18±0.04*#	0.14±0.02*#
	Cardiac muscle	1.02±0.18	0.69±0.16	0.48±0.12*	0.32±0.06*	0.26±0.04*#	0.18±0.02*#	0.12±0.02*#

Note: * – $p<0.05$ – the significant differences of the investigated indexes compared with the analogous data in control rats ($\chi 2$ test). # – $p<0.05$ – the significant differences of the investigated indexes compared with the analogous data in rats' pups before irradiation ($\chi 2$ test).

Thus, the data obtained demonstrate a wide range of pathophysiological muscle dysfunctions in response to medium-lethal doses of ionizing radiation impact. Both skeletal and cardiac muscles functional disturbances in such specified pathological conditions are characterized by muscle structural unit dysfunction – the actomyosin junction and an energy supply necessary for muscle contraction diminishing which in our trials was highlighted by an ATPase enzymatic activity significant decrease.

We emphasize that they are in a certain relationship with the results of a certain scientific works which proved the existence of an adaptation-compensatory reorganization of the body depending on the post-radiation period duration after the ionizing radiation small doses impact [5, 14]. While discussing our data we consider it reasonable to settle the following.

Firstly, we focus on the methodological background of our trials according to which we investigated the muscle activity pathophysiological dysfunctions in the descendents of irradiated animals after exposure to radiation. We consider this rational taking into account the importance of expressed radiation-induced muscle disorders pathogenetic mechanisms detailed studying which is possible in the descendants of previously irradiated biological organisms.

Secondly, the data obtained should be approximated to the biological organism taking into account the biochemical nature of the radiation direct harmful impact on the biological organism. Thus, it's important to understand that along with the destructive/alterative influence on the organism due to the ionizing radiation interaction with the biological body, there are also reverse reactions in the form of both atoms and molecules recombination and polymer chains restoration. As a result of such reactions, both primary and new or modified forms of the substance can be formed, which is the leading pathogenetic mechanism of ionizing radiation impressive impact on human organs and tissues, the detailed mechanisms of which have not yet been sufficiently studied [1, 10].

We assume that muscle system functional activity restoration might be developed in the case of the body anti-radiation system functional activity enhancement, after the sanogenetic mechanisms activation. Our current research is aimed at radiation-induced muscle dysfunction pathogenetic mechanisms determination [14] and a scheme for radiation-provoked disorders pathogenetically based pharmacological correction development [3] which, additionally to the fundamental positions of pathophysiology, are two chains aimed to pathological radiation system activity suppression.

Thirdly, we note the important, in our opinion, aspect of the dose-dependent effect of irradiation on the muscle system functioning. Our data revealed that when sexually mature animals are irradiated by 0.5 Gy, the descendents have no expressed pathological changes within muscle system, but, on the contrary, one could see biosynthetic processes stimulation, the organism adaptive capabilities increasing which can be explained by "hormesis" phenomenon [9]. More expressed changes in contractile muscle proteins concentrations and intramuscular energy processes occur in the dsecendents when sexually mature animals are irradiated by the maximal dose. Therefore, ionizing radiation drastically reduces the irradiated offspring organism' compensatory and adaptive capabilities which is manifested in contractile proteins level expressed decrease and energetic ATP-ase activity minimization.

The next important, in our opinion, moment is the intramuscular enzymatic energetic activity changes dynamics. The ATPase activity is the leading functional characteristic of myosin and actomyosin which determines muscles contractile value [6, 7, 11]. The proved depression of skeletal muscles and myocardium Mg^{2+}, Ca^{2+}-ATPase and K^{+}-ATPase activity reflects the significant decrease of Mg^{2+}, Ca^{2+}, and K^{+} ions critically necessary for the myocyte membranes bioelectric processes appearance during the post-radiation period.

Thus, it is possible to draw schematically the following sequence of pathological processes pathogenetic chains induced by radiation exposure to biological organism: the influence of ionizing radiation → intramuscular metabolism dysfunction → intramuscular acidic metabolites (lactate and pyruvate) accumulation → intramuscular energetic biochemical reactions depression → ATP concentration and activity decrease → contractile muscle proteins concentration decrease → Mg^{2+}, Ca^{2+} and K^{+} ions concentration decrease, etc. The specified pathophysiological processes can develop sequentially and in parallel with the so-called "vicious circles" formation which fully explains the ionizing radiation induced muscle dysfunctions complexity, systematicity, inertia and time dependence.

The latter – our data highlight approximately comparable dysfunction of skeletal and cardiac muscles in the event of ionizing radiation exposure. Tissue respiration is well known to be suppressed after irradiation dose of 1.0 Gy. Therefore, deeper disturbances in skeletal and, especially, cardiac muscle bioenergetics should be expected with the dose of irradiation increase since the dominant way of intracardiac ATP refill is tissue respiration and phosphorylation In this case, the proven more alterative effect of ionizing radiation on cardiac muscle, additionally to pathophysiological relevance, indicates that the leading pharmacocorrective effect should be of radio- and cardioprotective action which will restore the myocardium energy sources.

Resuming the data obtained, we note that the leading links in the body and the muscle system radiation damage pathogenesis are the muscles functional state dysfunction, metabolic resources degradation, biochemical processes inversion, depletion of the energy supply of the muscle contractile function and the contractile intramuscular apparatus disruption. These pathological changes are characteristic to skeletal muscles and myocardium, are manifested in previously irradiated animals' descendents, are dose-dependent of irradiation and have a character dependent on the term of the post-radiation period.

The pathophysiological mechanisms of ionizing radiation induced muscle dysfunction are aimed to short-term and dose-dependent processes of biosynthetic mechanisms activation which strengthens the body's regenerative capabilities, reduces destructive intramuscular processes brutality and supports the skeletal and cardiac muscle contractile activity.

Conclusions

1. The ionizing radiation influence causes a disturbance in skeletal and cardiac muscles functioning in irradiated animals' descendents manifested by muscle structure structural unit dysfunction – the actomyosin junction.

2. Muscle contraction energy supply disturbance realized by ATP-ase enzymatic system activity significant decrease is one of the types of ionizing radiation pathological impact on irradiated animals' descendents.

3. A more alterative effect of ionizing radiation on the cardiac muscle has been proven.

4. The leading links in the body and the muscle system radiation damage pathogenesis are the muscles functional state dysfunction, metabolic resources degradation, biochemical processes inversion, depletion of the energy supply of the muscle contractile function and the contractile intramuscular apparatus disruption.

5. The core mechanism for radiation-induced muscle dysfunctions pathogenetically oriented scheme of pharmacological correction realization should be radioprotective and muscle-protective efficacy which will provide the opportunity to restore destroyed biochemical, physiological, electrical, functional and regulatory processes and activate sanogenetic mechanisms.

Prospects for further research include a further investigation of pathogenetically oriented pharmacological correction efficacy investigation in the organisms of the irradiated animals descendents aimed to the muscle functional activity reestablishment after ionizing irradiation impact.

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