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EFFECTS OF EXTRACT OF LICORICE ROOT ON LIPID PEROXIDATION SYSTEM IN RATS DURING LONG-TERM INHALATION OF SMALL AND LARGE DOSES OF URANIUM ORE DUST

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Abstract

Aims. The article is aimed at to describe effects of the extract of licorice root on lipid peroxidation processes in rats inhaling small and large doses of uranium ore dust.

Materials and methods. In healthy outbred male rats in different terms of inhalation of uranium ore dust (3-120 days) of different intensity (5, 10 and 50 MPC), the concentrations of malondialdehyde was assessed in their lung tissue and serum with and without oral administration of the LRE in 100 мг/kg of weight.

Results. Effects of the uranium ore dust in doses of 5 and 10 MPC during adaptive reactions the rise of the contents malondialdehyde in the lungs was insignificant and reversible. The 3.4-3.5-fold increase of malondialdehyde content in lung tissue was marked at 120th day, with the pattern of destructive disorders and the appearance of pathological submicroscopic changes. At uranium ore dust inhalation in a dose of 50 MPCs, consistent growth of malondialdehyde in the lung tissues begins at 7th day when heavy destructive changes begin.

The use of the licorice root in animals for a month after the entire period of inhalation of small doses of the uranium ore dust led to a slight decrease in malondialdehyde synthesis in pulmonary blood, but a sharp decrease in its release into blood. When exposed to the uranium ore dust at 50 MPCs, administering the licorice root had a significantly positive antioxidant and antitoxic effect, delaying lipids peroxidation in lung tissue and their release into blood.

Conclusion. The oral administration of the licorice root to rats exposed to different doses of the uranium ore dust has positive, antioxidant and antitoxic effect, reducing the synthesis of lipid peroxidation products in lung tissue and their release into blood.

Keywords: *uranium ore dust, lipid peroxidation processes, lung tissue, serum, malondialdehyde, rats, licorice root extract.*

Introduction

One of the basic mechanisms of ionizing radiation action on the structure of the body's tissues is the activation of free radical processes. Significant changes in the metabolic processes are most pronounced in the organs of deposit of radioactive elements (Einor D et al., 2016; Ivanitskaya NF, 1992).

Defeat by ionizing radiation and the imbalance of adaptive systems are expressed by oxidative stress induced by the reactivity of free radicals of oxygen. One of its key organic features is the lipid peroxidation (LPO) (Einor D et al., 2016; Mikkelsen RB et al, 2003; Nathan C et al., 2013). In the last stages of decay of endoperoxides generated during the intramolecular rearrangements in the structure of the fatty acids, malondialdehyde (MDA) is formed. In this regard, the MDA can be used as an indicator of the extent of the LPO and oxidative stress of the body tissues (Spirlandeli AL et al., 2014).

At present, aggravated global radioecological situation and expanded occupational health risks lead to the increase in the risks of oxidative stress. It actualizes the search for and evaluation of protective means against

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multiple (fractional) and chronic exposures. In addressing this problem, the important role belongs to search for long-acting radioprotective agents among substances of natural origin: animal and herbal remedies (Arora R. Et al., 2005; Dutta A et al., 2012; Khan AA, et al., 2016). A range of natural remedies with radioprotective properties is studied and proposed to use (Hosseinimehr SJ, 2007; Koukourakis MI, 2014).

In this aspect, it is of interest to study the radioprotective activity of licorice root (Fukuchi K, et al, 2016).

The main studied compounds are licorice glycyrrhizin and glycyrrhetic acids and their derivatives contained within 8-24% (Akao T., 2000a; Shabkhiz MA, et al., 2016). Apart of glycyrrhizin, licorice consists of 27 flavonoids, glucose, sucrose, starch, fiber, resinous, bitter and ashy substances (Akao T, 1999). Licorice flavonoids are Liquiduritin, isokliviritin, likurazid, isoglabraside, rhamnolikviritin, ramenoisoliquiritin, neolikviritin, glyphoside, uraloside and others. Licorice flavonoids are comprised of flavonols, chalcones and their isoforms (Akao T, 2000 b).

After the discovery of its deoxycorticosteroid effect, licorice preparations became very important. As a part of licorice, glycyrrhetic acid is a synergist of cortisone and it has potent anti-inflammatory activity (Dhingra D, et al, 2004; Fogelman Y, et al., 2016; Fukuchi K, et al, 2016). Certain antileukemic activity of both the glycyrrhetic acid and its derivatives is defined. In some studies, anti-toxic and antimicrobial action of licorice root against toxins diphtheria, tetanus, nicotine, mercuric chloride and staphylococcus aureus, tuberculosis mycobacteria and fungi discovered (Karimov MM et al., 2000; Gabriel AA et al, 2014; Antolak H et al, 2017).

The literature shows that licorice ranks as one of the first among all known medicinal plants in the world, leaving ginseng, and Golden root (Rhodiola rosea) behind (Li IA et al, 2003).

Despite the wide range of studies of the use of medicinal products extracted from licorice root, there is no posts about the impact of licorice on the function of the respiratory system in the conditions of uranium poisoning in available literature.

Given the rich variety of medicinal properties of licorice root extract (LRE), in our work we set out to study its effect on systems of lipid peroxidation in animals exposed to small or large doses of uranium ore dust (UOD).

Materials and Methods

Study material and protocol. The experimental part is carried out on 228 white male rats with initial weight 140-180 g divided into 8 groups:

№ 1 - group of the initial control - 24 rats
№ 2 - group of the control for other 6 experimental groups - 72 rats
№ 3 - experimental group received UOD dose of 5 maximum permissible concentrations (MPC) (10.775 mg/m^3) by inhalation – 36 rats
№ 4 - UOD dose of 10 MPCs by inhalation (20.55 mg/m^3) – 36 rats
№ 5 - UOD dose of 50 MPCs by inhalation (107.75 mg/m^3) – 36 rats
№ 6 - UOD dose of 50 MPCs by inhalation (107.75 mg/m^3) and simultaneous treatment with licorice root extract - 36 animals
№ 7 - UOD dose of 5 MPCs (10.775 mg/m^3) and LRE treatment for 30 days - 36 animals
№ 8 - UOD dose of 10 MPCs (20.55 mg/m^3) and LRE treatment for 30 days - 36 animals.

Inhalation exposure of animals by the UOD was carried out in special primer chambers UIP-1. Their design provides an easy approach to force air directly into respiratory airways. The dust concentration in primer chamber air was kept homogeneous and constant. Uranium dust from the Stepnogorsk mining and chemical plant was applied to the primer. The chemical structure of the dust is described in the following percentages: U – 0.332; Mo – 0.082; Zn – 0.020; Fe – 4.27; SiO_2 – 40.60; Al – 2.44; As – 0.006; Mn – 0.14. The total α-radioactivity of the dust was 202 Bq/g. The MPC of the dust for a working zone air is 2 mg/m^3.

The experiments were carried out for 4 hours each day in a 5-day work week, continuously for 120 days at doses 5 and 10 MPC, and within 60 days at the dose of 50 MPC. A separate group of animals (№6) was exposed to the UOD in the dose of 50 MPC for a week prior to the beginning the experiment, and then during the study were treated with 2 ml of the licorice root extract (LRE) per os (calculated on the base of 100 мг/kg of weight). To study modifying effect of the LRE on post-radiational changes of LPO and antioxidative protection system of rats exposed by small doses of the UOD (5 and 10 MPC), animals of 7th and 8th groups after termination of the UOD primer were administered

per os by the LRE during 30 days. The total study length was 150 days. In all cases, the control group of animals was investigated according to the research terms. In addition, 6 animals-intact rats comprised the initial control.

The primer conditions and duration of the research were conducted in accordance to the WHO recommendations (ICLAS. Requirements…, 1978; WHO. Principles and methods…, 1981; International Recommendations…, 1993).

Bioethical considerations. The design and protocol of experimental studies were approved by the local bioethical committee of the JSC " Astana Medical University".

Determination of MDA in lung tissues. Spectrophotometric measurement of MDA was developed by Stalnaya ID and Garishvili TG (1977). At a high temperature in acidic medium, MDA reacts with 2-thiobarbituric acid to form a colored trimethine complex with an absorption maximum at 532 nm. The tissues were pre-homogenized. 2.5 ml of homogenate was transferred to centrifuge tubes and protein was precipitated by the addition of 1 ml of 17% trichloroacetic acid solution.

The resulting precipitate was separated by centrifugation for 10 minutes at 4000 rpm. 2 ml of the supernatant were transferred to tubes, 1 ml of 0.8% thiobarbituric acid solution was added and the samples were placed for 10 minutes in a boiling water bath. As a control, samples containing buffer solution (pH=7.4) instead of the supernatant. After developing the pink color, the samples were cooled and the optical density was measured against the control sample at 532 nm. The value of the molar extinction coefficient was used in the calculation.

Detection of serum MDA. Spectrophotometric

TABLE 1.

Changes of the malondialdehyde (MDA) content (μmol/g) in lung of rats inhaling uranium ore dust (UOD) in doses of 5, 1 0 and 50 MPCs.

Group of rats	Dose of UOD	Experiment terms (days)						
		3	7	30	60	90	120	150
Intact rats (Norm)		392.6±79.6	394±11.0	392.6±19	394±11.4	393±15.2	393±15.2	
Intact rats (control group)		393.6±19.0	394±11.8	391.5±15.0	395.8±11.2	393.6±11.4	392±10.8	
Exposed to UOD (experiment)	5 MPC			720±22.0*	560±24.0*	570±90.0*	1350±90.0*	
	10 MPC			660±26 * (n=6)	580±37 * (n=7)	530±13 (n=6)	1400±4.6 * (n=6)	
	50 MPC	305.9±22*	961.5±10.6*	1105±39.2*	1248.5±15.6*			
Deviation from the control group (%)	5 MPC			+83.2	+42	+44.7	+242.6	
	10 MPC			+65.4	+47.2	+37.5	+257.3	
	50 MPC	-32.4	+143	+180	+216.7			
Deviation at 3rd day			>3.1 fold	>3.6 fold	>4.1 fold			
Exposure to UOD + Extract of licorice root	5 MPC							1310±80.0**
	10 MPC							1100±34§
	50 MPC	158.1±14.8§	609.0±9.6§	484.6±40.0§	811.0±64.2**			
Deviation from the control group (%)	10 MPC							+232.4
	50 MPC							+180.6
	5 MPC	-60	+54.6	+23	+105.8			
Deviation from the norm (%)	50 MPC	-48.2	-36.7	-56	-35			

*- Is authentic in comparison with norm, $p<0.05$

** - is authentic in comparison with the control, $p<0.05$

§ - Is authentic in comparison with norm and with the control, $p<0.05$

measurement was proposed by Chevari S, Andyal T and Pandel A (1992). The principle of method based on the detection of MDA in the reaction with thiobarbituric acid. 0.5 ml of a 20% solution of trichloroacetic acid was added to 0.1 ml of blood serum and intensively stirred and centrifuged for 10 minutes at 3000 rpm. The supernatant was separated, to which 1 ml of a 0.67% solution of thiobarbituric acid was added. Optical density was measured against the control at a wavelength of 532 nm in a cuvette with 10 mm of optical path length. The optical density of the standard solution is about 0.650-0.700. The calculation was made using the formula: E_{act}/E_{st}•440=μmol/l of MDA

Statistical Analysis. Comparisons between experimental groups and relevant controls were performed by Student's t-test. Significance of differences was tested using ANOVA, with $P<0.05$ as the limit of significance.

Results

Dynamics of MDA in lung tissue and serum of rats exposed to UOD doses of 5, 10 and 50 MPCs are shown in Tables 1 and 2.

Exposed to UOD in a dose of 5 MPCs. As seen from the Table 1, on 30s day the MDA content in lung tissue was increased by 83. 2%. On 60th and 90th days, the MDA concentration was different from the control by 42 and 44% respectively, but the increase was two times lower than in the first period of observation. The highest concentration was found on 120th day from the start of priming, when the MD§§A level in lungs is increased 3.4 times.

In serum of this group rats, the MDA content was fluctuating during the all experiment, rising by 40% in the 1 and 3 months, then decreasing slightly on 3 and 4 months (Table. 2). Nevertheless, the MDA level in all observation periods was steadily increasing without tendency to further increase.

Under these conditions, the introduction of licorice root extract (LRE) in experimental animals did not influence on quantitative indicators of MDA in lung tissue, but significantly reduced the release of the tested endotoxin into blood 3.2 fold.

Exposed to UOD in a dose of 10 MPCs. Dynamics of the MDA content in lung tissues of inoculated rats was uneven, with a tendency to in-

Table 2.

Changes of the malondialdehyde (MDA) contents in blood rats (μmol/l) inhaling uranium ore dust (UOD) in doses of 5, 10 and 50 MPCs

Group of rats	Dose of UOD	Experiment terms (days)						
		3	7	30	60	90	120	150
Intact rats (Norm)		3.6±0.3		3.6±0.3				
Intact rats (control group)		3.6±0.11	3.5±0.10	3.9±0.08	3.7±0.06	3.65±0.2	3.6±0.11	
Exposed to UOD (experiment)	5 MPC			5.1±0.09	4.8±0.16	5.03±0.32	3.2±0.32	
	10 MPC			3.7±0.04	2.6±0.35	2.3±0.11	3.8±0.31	
	50 MPC	5.6±0.31*	6.5±2.1*	3.0±0.3	3.3±0.3			
Deviation from the control group (%)	5 MPC			+41.7	+33.3	+39.7	-11.1	
	10 MPC			+2.7	-28	-36	+5.5	
	50 MPC	+55.5	+80.5	-16	–			
Exposure to UOD + Extract of licorice root	5 MPC							1.10±0.01**
	10 MPC							0.89±0.11*
	50 MPC	3.8±0.08**	2.8±0.5**	1.6±0.2**	2.3±0.2**			
Deviation from the control group (%)	5 MPC							-69.4
	10 MPC							-75.2
	50 MPC	-32.2	-20	-54	-30			
Deviation from the norm (%)	50 MPC	-5.5	-22.2	-110	-36			

*- Is authentic in comparison with norm, $p<0.05$

** - is authentic in comparison with the control, $p<0.05$

crease (Table 1). By the end of the 1st month, its content has increased by 65.4%, dropping to 3rd and even more to the 4th month of the experiment. But still MDA in these periods were higher than normal concentration of 47.2% and 37.5% respectively. By the end of 4th month of inhalation, the concentration of MDA in the lungs exceeded the normal rate 3.5 times.

It did not differ from the normal values in the serum at the end of 30 days of exposure concentration of MDA. After 60 and 90 days, the MDA level decreased by 28% and 36% respectively, with insignificant fluctuations in the remaining period of observation.

The introduction of the LRE to animals of this group after 4 months of exposure decreased significantly the release of investigated endotoxin in the blood - 4.3 times.

Exposed to UOD in a dose of 50 MPCs. The content of MDA in lung tissue of animals in this group to the 3rd day of the experiment is not changed (Table 1), although the release into the blood increased by 55.5% (Table. 2). On the 7th, 30th and 60th day of the UOD inhalation, the MDA concentration in the lung tissue is increased in 2.4, 2.8 and 3.2 times compared to the norm, indicating a dose-time dependence of the observed change. Simultaneously it was found that on the 7th, 30th and 60th day of the exposure to the UOD, the MDA level in the lung tissues was 3.1, 3.6 and 4.1 times greater than on the 3rd day of observation. The MDA level in serum is also increased (to 80.5%) to the 7th day but by 30th day it was below the normal value, remaining low until the end of the experiment (Table 2).

The application of the LRE to rats exposed to the UOD in the dose of 50 MPCs led to reducing the MDA content in pulmonary tissue by 2 times (48.2%) and the release in blood by 30% on 3rd day of inhalation. On 7th day, the reduction was 36.7% in the lung tissue, and 57% in the blood serum. On the 30th day of the experiment, the LRE decreased the MDA concentration in the lung tissues and serum by 56% and 47%, respectively. On 60th day, the MDA level dropped in the lungs by 35%, and in the blood by 32.2%.

Thus, in the first three months of the UOD exposure by 5 and 10 MPC doses the MDA level in the lungs remained relatively steady increased and only on 120th day of the experiment, its level increased by 3.4 and 3.5 times regardless of dose. During the UOD exposure at 50 MPCs, the increase the MDA content of MDA in the lungs was in a direct relationship with duration of exposure, and took a regular character, emphasizing the prognostic significance of their changes (Tables 1 and 2).

DISCUSSION

Prolonged exposure of polymetallic dust containing natural radionuclides causes the activation of lipid peroxidation and some change in the activity of antioxidant enzymes in animals (Shaimardanova GM, 2009). They may be as a pathogenetic basis for ultrastructural damage of lung cell elements, accompanied by morphological and functional disorders of organs and systems (Baraboy VA et al, 1997; Jumasheva RT et al, 2008; Jumazheva RT et al 2009).

Oxidants cause structural damage in lungs, act on fibroblasts, reduce the activity of the surfactant, stimulate the formation of thromboxane, increase epithelial permeability, and impair ciliary function, and etc, i.e. they mediate many processes that favor the development of the pathological process in the lungs.

In principle, any organs and tissues can suffer from oxidative damage. However, the lungs are most vulnerable in this respect, since they increase the possibility of free radical reactions. Unlike other organs, the lungs are directly exposed to oxygen - the initiator of oxidation, as well as oxidants contained in polluted air (ozone, nitrogen and sulfur dioxides, etc.). Lung tissue comprises in excess of unsaturated fatty acids, which substrates the LPO (Zenkov NK et al, 2001). The lungs are directly affected by the whole complex of toxic substances contained in the air. All these substances activate phagocytic cells that secrete active forms of oxygen, and then the process of free-radical oxidation (Osipov AN et al, 1990). Protection against the damaging effects of the LPO is provided first of all by special antioxidant enzymes: superoxide dismutase, catalase, peroxidase, glutathione enzymes redox-system. Normally, in the oxidant-antioxidant system some balance is maintained (Kogan AH et al, 1987; Fattal AL et al, 1989). Breaking this balance in favor of oxidants results in the development of so-called oxidative stress (Russanov E et al, 1979; Kotelevtseva NV, et al, 1980; Fattal AL et al, 1989). Violation Breaking stationarity of processes of free radical oxidation

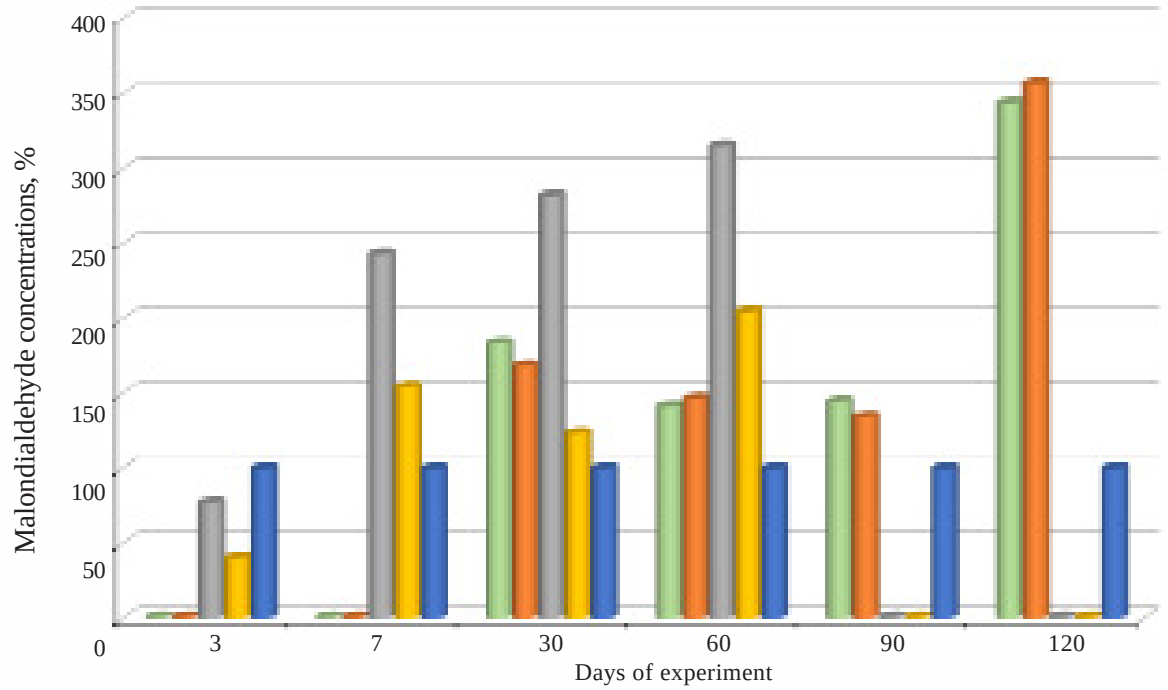

Figure 1. *Dynamics of the MDA concentration in lung tissues of rats exposed to different doses of uranium ore dust and treated by Licorice root extract*

Note: Обозначение доз - 5MPC; 10 MPC, 50 MPC; 50MPC+LRE, Control

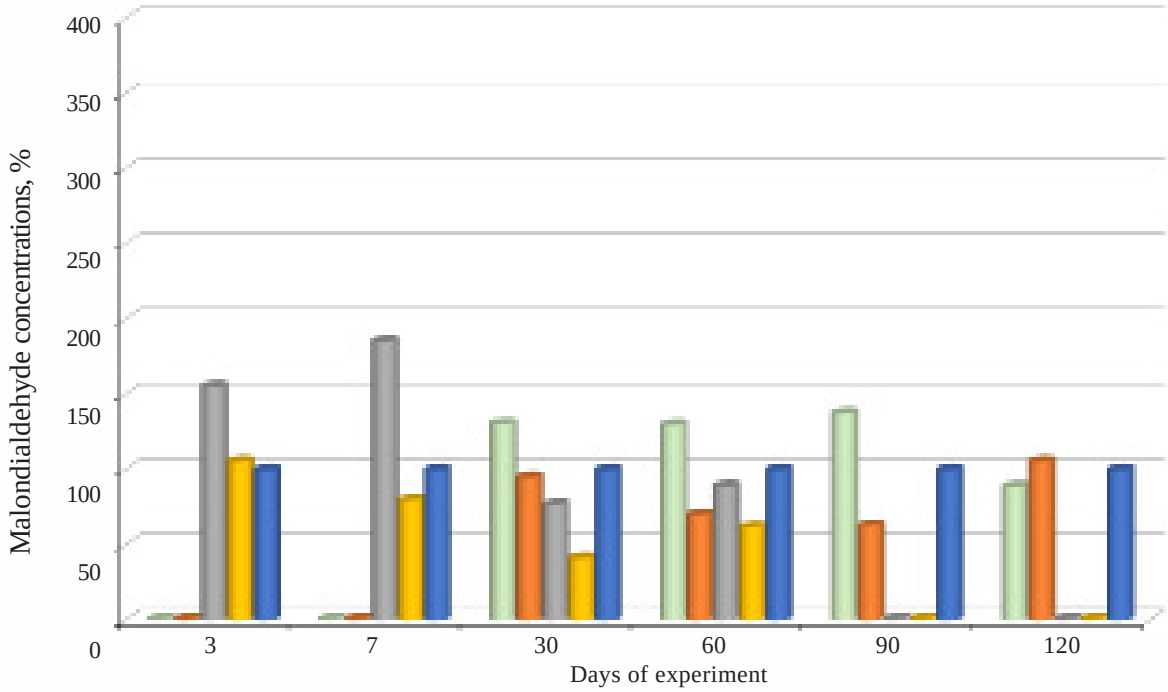

Figure 2. *Dynamics of the MDA concentration in blood serum of rats exposed to different doses of uranium ore dust and treated by Licorice root extract.*

Note: Обозначение доз - 5MPC; 10 MPC, 50 MPC; 50MPC+LRE, Control

is now regarded as a universal, non-specific mechanism of pathogenesis underlying various diseases (Russanov E et al, 1979).

In our studies, dynamics of the MDA content was traced in rats exposed to the UOD, generally evaluating the POL system.

The results of a series of studies, it is clear that the nature of responses of the lung tissue to the UOD exposure in doses of 5 and 10 MPC was of the same type. In the end of the 1st month, the MDA level of the UOD exposure increased against the norm by more than 1.5 times in both groups. In the next 2 or 3 months, signs of increased MDA content in the lungs are persisted, but the level of its increase was 2 times lower than in the 1st month of observation. Sharp excess of normal values in 3.4 and 3.0 times, respectively, have been identified by the end of the experiment, on the 120th day of the UOD exposure. Therefore, even in the ultra-low dose of 5 MPCs after 4 months of the UOD exposure, the synthesis of MDA and its release into the bloodstream are increased more than 3 times. But this increase was stable in all periods of observation without any tendency to a natural increase. Therefore, the time threshold of the primer in 4 months is critical. Marked changes, undoubtedly, indicates that on the basis of the synthesis of MDA in lungs, analyzed doses of 5 and 10 MPCs should be classified as ultra-low doses. Within 2 months of the UOD exposure, no observed restructuring of the membrane system of lung tissue cells takes place.

In contrast, with increasing UOD doses up to 50 MPCs, regular increase of MDA in lung tissue is detected already on 7th day, accompanied by a sharp increase in its emission in the blood. On 30th and 60th, the MDA concentration in lung tissue exceeded normal values 2.8 and 3.2 times, respectively. Consequently, with increasing doses of damaging factor to 50 MPCs, the stable damage of cell membranes occured on 7th day reaching almost triple values by the end of the 1st month of the exposure. Under these conditions, changes indicated the presence of a dose-time dependence of damaging effect of radioactive UOD on the cell membranes and processes of accumulation of the analyzed LPO product in the lung tissue (Fig. 1 and 2).

As can be seen from Figure 1, in the beginning of the UOD exposure in doses of 5 and 10 MPCs, when the compensatory-adaptive responses take place, the increase of the MDA content in the lungs was negligible, not exceeding 65-83%, and was reversible. Particularly sharp rise in the MDA level in the lung (in 3.4-3.5 times) on 120th day draws attention, when the destructive pattern of damages was registered with the advent of submicroscopic pathological changes in the lung tissue according to morphological, morphometric and electron microscopy studies (Jumasheva RT, et al, 2009). Increasing doses of the UOD up to 50 MPCs has led to the growth of MDA in lung tissue that began already on the 7th day, when started heavy destructive changes described earlier (Jumasheva RT et al, 2008).

The application of the LRE in animals for one month after all inhalation period of low UOD doses (5-10 MPCs) resulted in a slight decrease in the synthesis of MDA in the pulmonary blood but in a sharp decrease in its release into the bloodstream. And the LRE administration during the exposure by the UOD of 50 MPCs had significantly positive, antioxidant and anti-toxic effect, delaying the synthesis of the LPO metabolites in the lung tissue and its release into the blood.

CONCLUSION

Thus, oral administration of aqueous LRE to rats in a dose of 100 mg/kg for a month after the entire period of inhalation of low doses of the UOD (5-10 MPC) resulted in a slight decrease in the synthesis of MDA in the pulmonary blood but in a sharp decrease in its release into the blood. The application of the LRE during inhalation of 50 MPCs dose of the UOD had a significantly positive, antioxidant and anti-toxic effect, reducing the synthesis of the LPO metabolites in lung tissue and their release into the blood.

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