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STUDY OF RADIOPROTECTIVE PROPERTIES OF E.COLI METABOLITES

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Abstract

Objective of this research was the development of a radioprotective drug on the basis of E.coli metabolic products (MP). The first stage of the research involved studies on the design of potential radioprotective drugs with the use of biologically active substances - biosurfactants expressed in the culture liquid (CL) during E.coli cultivation in liquid media. It was considered upon designing the radioprotective drug that E.coli metabolic products (endo-, exokines, enzymes, amino acids), along with antibacterial effect, have radioprotective properties. Subject to the above, we prepared 5 variants of radioprotective compositions: 1) E.coli bacterial mass with culture liquid + 90 cm^3 + 10 cm^3 of 6% aluminum hydrosilicate solution; 2) bacterial mass with culture liquid + 90 cm^3 + 10 cm^3 of 2% aluminum hydroxide solution; 3) culture liquid with a biomass 99.5 cm^3 + 0.5 cm^3 of 40% formalin solution; 4) culture liquid 90 cm^3 + 10 cm^3 of 6% aluminum hydrosilicate solution; and 5) culture medium 90 cm^3 + 10 cm^3 of 2% aluminum hydroxide solution.

The above compositions were tested at the next stage for radioprotective activity on various types of animals exposed to lethal ionizing radiation. The experiments involved 120 white mice of 18-20 g body weight, divided into 12 groups, each of 10 animals. Severe radiation disease was simulated through a single external exposure on a gamma-ray unit "Puma" at a dose of 7.7 Gy (LD_{100}). The test drugs were applied 24 hours before and 24 hours after irradiation. The results of these studies showed that the composition No.1 of 5 tested variants of the potential radioprotectors had the highest radioprotective activity, which ensured 80% survival of the irradiated animals after its single subcutaneous administration to animals 24 hours before and 24 hours after irradiation.

The results obtained in the experiments on white mice were verified in the following series of experiments on 99 white rats (radiation dose - 9.0 Gy) and 69 rabbits (11.0 Gy).

The formation mechanism of radioresistance in animals during treatment with E.coli metabolic products is conducted through inhibition of the pancytopenia and myelosuppression, and the correction of function of the cytokine, prooxidant-antioxidant system and a system of immunohemopoiesis.

Keywords: E.coli metabolic products, biosurfactants, gamma-rays.

1. Introduction

Along with the use of chemical radioprotectors, an increasing attention of scientists has been attracted by biological radioprotective means, since they have a number of advantages, such as the duration of the protective effect lasting several days and weeks rather than hours, without causing any negative side effects.

Among the effective bioradioprotectors are specific stimulators of immune responses such as vaccines, bacterial cultures and their components (polysaccharides, polypeptides) (M.V. Vasin, 1999). Positive radioprotective effect was observed after pre-exposure administration of the killed corpuscular vaccine of Gram-positive and Gram-negative bacteria (Behling U., 1983). The best results were obtained with the polysaccharide and lipopolysaccharide components of the intestinal bacterial group (R.S. Budagov; L.P. Ulianova; 2001; L.M. Surgucheva, 2002; Ainswozth E., 1989).

The results of long-term radiomicrobiologic studies show that one of the main enemies of the irradiated organism is autoflora leading to the colonization of the internal organs with microbes and causing post-radiation development of endogenous infection due to a sharp decline in immunobiological reactivity, which is essential in the development of methods and means of diagnosis, treatment and prevention of radiological injuries (A.V. Ivanov et al., 2008).

This key statement, established by the radiation immunologists and microbiologists, has served as the basis for the development of a radioprotective E.coli polyagent by the staff of FSBSI “Federal Center of Toxicological, Radiological and Biological Safety - All-Russian Scientific and Research Veterinary Institute” and its further use for the specific prevention of radiation injuries of the body (Patent RU №2226106, 2004), which was further improved by G.I. Rakhmatullina. (Patent RU №2338546, 2008).

The designed production technology of the radioprotective E.Coli polyantigen ensured 70% protection of the body from the lethal radiation upon its prophylactic use, however, its use for therapeutic purposes aggravated the course of acute radiation sickness (ARS), which is due to the presence of living microbial cells in its composition. Furthermore, the polyantigen production technology involves cultivation of the microbes on solid culture medium, which was rejected after flushing the biomass, thereby greatly increasing the cost of the final product.

However, it is known from the literature that microorganisms during their growth in liquid culture medium express a unique set of bioactive substances (enzymes, antigens, exo- and enterotoxins, and antibacterial agents) (E.I. Tkachenko et al., 2005), which individually and in various combinations have radioprotective effect (R.N. Nizamov et al., 2010).

Subject to the poor knowledge of the studied problem and due to its relevance, we have conducted these studies.

2. Materials and Methods

The experiments involved 595 animals, including 412 white mice of 18-20 g body weight, 99 white rats of 180-200 g body weight, and 69 rabbits of 2.0-2.5 kg body weight.

One production (E.coli, st. PL-6, No. 1154115, the causative agent of colibacillosis-induced diarrhea in piglets) and 3 epizootic (E.coli, st. UK-2, No. 1153/15, the causative agent of piglet diarrheas; st. PZ-3, No. 1150/15, the causative agent of calve diarrhea; st. KV-1, No. 1156/15, the causative agent of piglet colibacillosis) strains, obtained from the museum strain collection of FSBSI "Federal Center of Toxicological, Radiological and Biological Safety - All-Russian Scientific and Research Veterinary Institute", were used as test-microorganisms.

In our experimental studies on the cultivation and study of the enzymatic properties of the producing strain we used liquid (BEB Hottinger's broth, PEUH medium) and dense (BEA, blood agar, a set of culture media with lactose, mannitol, glucose, sucrose, gelatin, citric-ammonium medium, Simmons medium, and ferrous sulfate agar) culture media recommended by the XI State Pharmacopoeia (1990) and the Guidelines for preclinical research methods of pharmacological substances (2000).

As potential radioprotective agents we used 72 variants of culture liquid obtained from the above culture media at different time (after 18h, 24 h, and on day 3, 4, 5, 6, 7, 8, 9, and 10) of the producing strain cultivation, and as control health-promoting drugs we used the radioprotective polyantigen and the anti-radiation health-promoting immunoglobulin. Radiation injuries were simulated in animals with the use of a gamma-ray unit "Puma" with ^{137}Cs radiation source and the irradiation dose of $3.13x10^{-5}$ Cl (kg*s). The microbiological and immunological studies used standard solutions, the appropriate chemical reagents, sera, antisera, antigens, instruments and equipment (refrigerators, thermostats, water baths, centrifuges, spectrophotometers, etc.). Studies on the production of microbial metabolic products was carried out on the basis of E.coli strain SP-6, producing a complex of biologically active substances. Cultivation of the E.coli strain SP-6 for the production of metabolic products was carried out on a liquid medium in accordance with conventional methods. The main qualitative indicators of the obtained variants of culture

liquid were pH, biomass yield, cell concentration, and the catalase (CT), peroxidase, superoxide dismutase (SOD), formate dehydrogenase (FDG) and antibacterial (ANB) activity. Based on E.coli metabolism products and natural minerals (hydrous silicate and aluminum hydroxide) the radioprotective compositions were designed: 1) culture liquid, containing 2*109 m.c./cm^3 - 90 cm^3 + 10 cm^3 6% aluminum hydrosilicate (AHS) solution; 2) culture medium with the bacterial mass ($2*10^9$ m.c./cm^3 - 90 cm^3 + 10 cm^3 of 2% aluminum hydroxide (AH) solution; 3) culture liquid with a biomass 99 cm^3 + 0.5 cm^3 of 40% formalin solution; 4) culture liquid with a biomass 99 cm^3 + 10 cm^3 of 6% AHS solution; and 5) culture liquid with a biomass 90 cm^3 + 10 cm^3 of 2% AH solution. For complete conjugation, the above compositions were placed in a thermostat at a temperature of 37^oC at constant stirring in a shaker, incubated for 30 minutes, and then subjected to radiation sterilization with a gamma-ray unit “Issledovatel" at a dose of 7000 Gy and used further as potential radioprotective agents. Before testing the radioprotective efficacy, the resulted drugs were verified for sterility, safety and allergenic effect in accordance with standard pharmacological and microbiological methods. Test for health-promoting action of experimental samples of the culture fluid was performed on the 7.7 Gy (white mice), 9.0 Gy (white rats) and 11.0 Gy (rabbits) irradiated laboratory animals receiving a single dose of test drugs s/c at a dose of 10-50 mg/kg dry matter 1-10 days before and 1-10 days after irradiation.

The efficacy of drugs was assessed by clinical-hematological and immunological parameters, ARS course, survival rate and duration of life expectancy of dead animals. Upon assessing the hemoprotective effect of drugs, the amount of hemoglobin, red blood cells, white blood cells, lymphocytes, platelets, color index and leukogram were determined by the conventional techniques of radiation hematology. Serum concentration of cytokines was determined by immunoenzyme method with the use of "Mouse KSF”, "Mouse IL-I”, and "Endogen” kits, USA.

3. Results

During the first series of experiments, the radioprotective activity of drugs based on E.coli and its metabolites was assessed on 120 white mice of 18-20 g body weight, divided into 12 groups, each of 10 animals. First five groups of animals were subcutaneously received single-dose drugs 1, 2, 3, 4, 5, respectively, at a dose of 0.1 cm3, 24 hours before irradiation.

Other five groups of animals received the drug 24 hours after irradiation. Animals of group 11 and 12 received no drug and served as the irradiation control and biological control, respectively. Experiments were performed in triplicate.

Table-1. Survival rate of white mice irradiated at a dose of 7.7 Gy, based on dosing scheme.

Variant of the experiment	Dosing schedule	Live quantity, anim. units	Results			ALE, (days)
			died, anim. units	survived, anim. units	survival rate, %	
1	drug 1 single s/c administration 24h before irradiation	10	2	8	80	12.8
2	drug 2 single s/c administration 24h before irradiation	10	4	6	60	13.1
3	drug 3 single s/c administration 24h before irradiation	10	2	8	80	11.9
4	drug 4 single s/c administration 24h before irradiation	10	4	6	60	12.3
5	drug 5 single s/c administration 24h before irradiation	10	4	6	60	11.7
6	drug 1 single s/c administration 24h after irradiation	10	2	8	80	12.5
7	drug 2 single s/c administration 24h after irradiation	10	2	8	80	12.5
8	drug 3 single s/c administration 24h after irradiation	10	4	6	60	13.3
9	drug 4 single s/c administration 24h after irradiation	10	3	7	70	13.9
10	drug 5 single s/c administration 24h after irradiation	10	4	6	60	13.1
11	irradiation monitoring	10	6	-	0	6.9
12	biological monitoring	10	-	6	100	30

Note: s/c - subcutaneous administration

As can be seen from Table 1, the drug 1 based on the mixture of E.coli culture and culture fluid with the addition of 6% aluminum hydrosilicate, showed in both variants its radioprotective effect, protecting 80% of lethally irradiated animals from death. Similar results were obtained when repeating these variants on white mice in the series 2 and 3 of the experiments.

During the next series of experiments, we assessed the radioprotective efficacy of the drug 1 on 72 white rats of 150-180 g body weight, which were divided into 6 experimental and 6 control groups, each of 6 animals. The animals of

group 1, 2 and 3 received subcutaneously a single dose of drug 1 at a dose of 0.2 cm^3 10 days and 1 day before the lethal irradiation (9.0 Gy); the control animals (C_1, C_2, C_3) received microbial polyantigen (MPAG) at a dose of $2.3*10^9$ m.c./kg. White rats of group 4, 5 and 6 received the drug 1 at the indicated doses under similar conditions 24 hours and 5 and 10 days after irradiation. Control animals (C_1, C_2, C_3) received subcutaneously a single dose of anti-radiation health-promoting immunoglobulin (AHPI) at a dose of 50 mg/kg 24h after irradiation.

Test results of radioprotective effect of the drug 1 based on E.coli and its metabolic products on lethally irradiated white rats are shown in Table 2.

Table-2: Survival rate of the irradiated white rats (9.0 Gy) treated with drug 1 at different time before and after irradiation.

Group	Dosing schedule	Survival rate, %	ALE, day
1	Drug 1 single s/c administration 1 day before irradiation	66.6	12.0
2	MPAG single s/c administration 1 day before irradiation	16.6	11.7
3	Drug 1 single s/c administration 5 days before irradiation	66.6	13.5
4	MPAG single s/c administration 5 days before irradiation	50.0	11.1
5	group 3 - drug 1 single s/c administration 10 days before irradiation	83.3	14.2
6	MPAG single s/c administration 10 days before irradiation	66.6	12.7
7	Drug 1 single s/c administration 24h after irradiation	83.3	15.3
8	AHPI single s/c administration 24h after irradiation	66.6	13.1
9	Drug 1 single s/c administration 5 days after irradiation	66.6	12.9
10	AHPI single s/c administration 5 days after irradiation	50.0	10.9
11	Drug 1 single s/c administration 10 days after irradiation	50.0	12.1
12	AHPI single s/c administration 10 days after irradiation	33.3	8.9

The data in Table 2 show that both a preliminary (before irradiation) and subsequent (after irradiation) administration of drug 1 (E.coli cells suspension in culture liquid + aluminum hydrosilicate) has radioprotective effect, ensuring 50-83.3% survival of lethally irradiated white rats. The maximum radioprotective effect is observed upon administration of the drug 24 hours before and 24 hours after irradiation, ensuring 83.3% survival of lethally irradiated animals.

The positive results obtained from the experiments on two different species of laboratory animals have served as the basis for testing the drug on 72 Chinchilla rabbits of 2.0-2.5 kg body weight, which received subcutaneously the single dose drug 1 based on E.coli metabolic products and natural mineral 10, 5 and 1 day before and 1, 5 and 10 days after 11.0 Gy gamma-irradiation.

As a regulated radioprotective drug, we used a radioprotective polyantigen and an anti-radiation health-promoting immunoglobulin, administered at doses of $2*10^9$ m.c/kg and 50 mg/kg, respectively.

Blood samples were drawn in the animals both before and after irradiation to study the reaction of the blood system, cytokine and anti-prooxidant-oxidant systems to irradiation and application of the test radioprotector.

Test results of radioprotective effect of the drug 1 on lethally irradiated rabbits are shown in Table 3.

Table 3. Survival rate of the irradiated rabbits treated with drug 1.

Group	Dosing schedule	Survival rate,	ALE,
1	Drug 1 single s/c administration 1 day before	66.6	12.0
2	MPAG single s/c administration 1 day before	16.6	11.7
3	Drug 1 single s/c administration 5 days before	66.6	13.5
4	MPAG single s/c administration 5 days before	50.0	11.1
5	group 3 - drug 1 single s/c administration 10 days	83.3	14.2
6	MPAG single s/c administration 10 days before	66.6	12.7
7	Drug 1 single s/c administration 24h after	83.3	15.3
8	AHPI single s/c administration 24h after irradiation	66.6	13.1
9	Drug 1 single s/c administration 5 days after	66.6	12.9
10	AHPI single s/c administration 5 days after	50.0	10.9
11	Drug 1 single s/c administration 10 days after	50.0	12.1
12	AHPI single s/c administration 10 days after	33.3	8.9

Note: MPAG – microbial polyantigen; AHPI – anti-radiation health-promoting immunoglobulin; C_1 - control 1 (MPAG); C_2 - control 2 (AHPI).

As can be seen from Table 2, the test drug showed the maximum radioprotective effect at its emergency application (1 day before and 1 day after irradiation), ensuring 83.3% survival of lethally irradiated rabbits. Change in the period between immunization and irradiation led to a slight reduction in the radioprotective effect (16.7%), which is insignificant in comparison with the control drugs.

The results of hematological and biochemical studies have shown that the formation of radioresistance in lethally irradiated animals on the background of administration of the test drug based on E.coli and its metabolic products in combination with a natural mineral - aluminum hydrosilicate was achieved by inhibition of pancytopenia, preventing thereby the bone marrow devastation (Table 4).

Table 4. Effect of drug 1 on blood values of the 11.0 Gy irradiated rabbits.

Indicator	Biological monitoring	Irradiated	Preventively treated
Myelocariocytes	130.1±7.8	25.3±1.7*	109.6±11.7
Erythroid cells, $x10^{12}$/l	45.5±3.5	28.7±4.1*	46.0±3.1
Granulocytic cells, $x10^{9}$/l	63.3±3.8	8.1±0.7	52.3±5.2
Lyphoid cells, $x10^{9}$/l	16.9±1.7	1.5±0.3	14.3±3.3
Red blood cells, $x10^{12}$/l	5.3±0.8	3.9±0.1*	5.1±0.5
Reticulocytes, $x10^{9}$/l	125.3±11.9	78.9±7.5*	90.1±10.1
Platelets, $x10^{9}$/l	529.3±31.7	169.3±4.8*	401.3±15.4
White blood cells, $x10^{9}$/l	8.0±0.7	3.7±1.1*	7.1±0.3
Neutrophils, $x10^{9}$/l	9.3±0.7	1.9±0.5*	3.5±0.5
Lymphocytes, $x10^{9}$/l	4.7±0.3	1.1±0.3*	3.6±0.4

The prevention of pancytopenia and devastation of bone marrow during treatment with the test drug based on E.coli metabolic products was accompanied by increased synthesis of hemoregulatory cytokines: interleukin-1 (IL-1) and colony-stimulating factor (CSF) (Table 5).

Table 5. IL-1 and CSF levels in rabbit blood serum at different times after irradiation and drug administration (ng/ml).

Group	Post-exposure time, day					
	3		7		9	
	IL-1	CSF	IL-1	CSF	IL-1	CSF
Irradiated	4.9±0.7	1.5±0.3	2.1±0.1	0.4±0.09	_	_
Irradiated +	51.7±9.1*	28.9±4.9*	48.7±7.9*	21.3±5.9*	31.1±3.3	14.1±3.1
Control	23.0±1.9	7.3±1.3	17.5±3.2	9.9±2.1	9.9±2.1	17.3±1.9

*-P<0.001

Given that one of the mechanisms of hemototoxic effect of ionizing radiation is the apoptotic death of lymphocytes under the influence of radiotoxic substances - quinoid and lipid radiotoxins, it was interesting to study the state of prooxidant-antioxidant system of the body treated with the drug based on E.coli metabolic products.

The results of biochemical studies determining the concentration of lipid radiotoxins and antiradical enzymes (CAT, SOD) are shown in Table 6.

Table-6. MDA content, CAT and SOD activity in blood serum of the rabbits with ARS, receiving the drug 1 one day after irradiation.

Group	Study period, day	Indicator		
		MDA, µmol/l	CAT, mcat/l	SOD, U/l
Control	3	5.25±0.57	26.09±1.71	1.69±0.07
	7	5.43±0.59	25.95±0.57	1.70±0.05
	14	5.39±0.51	26.01±0.48	1.68±0.09
Irradiation	3	8.01±0.37*	11.95±0.49*	0.89±0.10*
	7	8.69±0.57	13.11±0.61	0.91±0.05*
	14	9.37±0.53*	14.01±0.43*	0.97±0.09*
Irradiation + drug	3	5.93±0.29*	21.05±1.09	1.25±0.07
	7	6.01±0.35	23.01±0.47	1.33±0.08
	14	5.83±0.21	24.79±0.57	1.41±0.11

Note: $P<0.05$

As can be seen from Table 6, a lethal irradiation of rabbits increased lipid peroxidation with further formation of malondialdehyde (MDA) and the reciprocal inhibition of the activity of antiradical enzymes SOD and CAT. A single subcutaneous administration of the drug 1 based on E.coli metabolic products inhibited the formation of toxic products of lipid peroxidation and maintained the activity of antioxidant enzymes (SOD and CAT) at the level of biological monitoring values.

4. Discussion

A direct comparison of radioprotective (survival test) hemostimulating, cytokin-stimulating and antioxidant (biochemical indicators) effectiveness of the five variants of E.coli metabolic products in conjunction with natural minerals, which was conducted within this study in the experiments on three different species of laboratory animals (white mice, white rats and rabbits), showed significant differences between them.

We have found that among the 5 tested variants the composition consisting of the E.coli microbial biomass, suspended in the liquid medium at a concentration of $2x10^9$ m.c./cm^3 in combination with natural mineral - aluminum

hydrosilicate at the rate of 2% to volume, showed the most expressed radioprotective activity. High radioprotective activity of the composition can be explained by the fact that this is a multi-component composition comprising both a cell and liquid fraction of the culture fluid and a natural mineral - aluminum hydrosilicate (bentonite), showing a versatile biological (anti-toxic, immunohemopoiesis-stimulating, antibacterial, and colicinogenic) effect, which ensures an increased radioresistance of the organism.

One of the mechanisms of effective radioprotection on the background of application of the studied composition is the maintenance of the number of erythrocytes, neutrophils, lymphocytes, i.e. the prevention of cell devastation of bone marrow, thymus and spleen.

Hemo- and myeloprotective effect of the drug on the basis of the E.coli metabolic products is carried out by controlling the composition of T- and B-lymphocytes, actively involved in the functioning of the hematopoietic microenvironment. The interaction of subpopulations of lymphocytes and macrophages is performed results in the synthesis and expression of the immunogenesis mediators - hemoregulating cytokines, such as interleukin-1 (IL-1), interleukin-3 (IL-3), colony stimulating factor (CSF), which are actively involved in the implementation of anti-radiation therapeutic effect (L.M. Rozhdestvenskii et al., 2012;. Dainiak N. et al., 2003;. Jarrett D.G., 2005; McVitte T.J. et al., 2005).

Another mechanism of enhancing the synthesis of hemoregulating cytokines in the radioprotection of the body during treatment with E.coli bacteria and their metabolic products is the presence of highly-molecular biologically active compounds in bacteria and E.coli culture fluid - surfactants, having probiotic and cytokin-producing properties (V.M. Lakhtin et al., 2010; T.A. Baeva et al., 2014; Kitamoto D. et al., 2002; Makkar R.S., Cameotra S.S., 2002; Maneerat S., 2005; Rodrigues L., 2006).

Given that the irradiation leads to the apoptotic death of lymphocytes under the influence of toxic products of oxidative modification – radiotoxins (V.I. Kapelko, 2003), it was interesting to study the state of prooxidant-antioxidant system of the lethally irradiated animals treated with the drug based on E.coli metabolic products.

It was found that the use of E.coli bacteria and their metabolic products in combination with a natural mineral - aluminum silicate ensured a modifying effect on the course of acute radiation sickness; inhibited the synthesis of TBA-active toxic radiolysis products - malondialdehyde (MDA); corrected the function of antioxidant protection by dismutation of autoperoxide radicals with the use of their interceptors - catalase and superoxide dismutase enzymes, which ultimately increased the survival rate of lethally irradiated animals.

Effective protection of the irradiated animals treated with the composition based on E.coli bacterial cells and their metabolic products was achieved due to the contained natural mineral - aluminum silicate (bentonite), which plays a dual role in the present composition.

The first is an active sorption of the expressed in the culture fluid E.coli cells and their metabolites (enzymes, amino acids, surfactants) by bentonite microparticles, which thereby forms a molecular “constructor" consisting of the attacking (targeting or therapeutic) and transport parts, combined in the form of an improved module having targeted action on the infected cell (K.N. Vagin, 2011). After reaching the irradiated target cell, a transport part of the module, due to the ion-exchange sorption and desorption ability of its molecules, cleaves and provides a targeting portion to the infected target cells of the macroorganism, actively sorbing the toxic metabolic products, exo-, endo- and radiotoxins, with their further clearance from the irradiated organism (R.R. Gainullin, 2009; Taylor D.R., 1999).

6. Summary

The evidence presented by the results of the study allow us to make the following conclusion.

Using the E.coli bacterial cells, their metabolic products and a natural mineral - aluminum hydrosilicate, we have designed a radioprotective composition with both preventive and therapeutic effect.

The experiments on lethally gamma-irradiated white mice (7.7 Gy) white rats (9.0 Gy) and rabbits (11.0 Gy) show high radioprotective activity of the composition in case of both preventive (1-10 days before irradiation) and therapeutic (1-10 days after irradiation) application, ensuring 66.6-83.3% survival of lethally irradiated animals.

The formation mechanism of radioresistance in animals during treatment with radioprotective compositions based on E.coli bacteria, their metabolic products and a natural mineral - aluminum silicate is conducted through inhibition of the pancytopenia and the myelosuppression, correction of the function of the cytokine, prooxidant-antioxidant systems and a system of immunohemopoiesis.

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