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Effect of The Rs-10 Radioprotector on Protein-Steroid Interaction in Irradiated Animals with Biphasic Adrenocortical Response to Irradiation

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Abstract— The article is devoted to the influence of RS-10 radioprotector on the protein-steroid interaction in irradiated animals. Introduction. Increasing threats to the radiation safety of the population is now causing the need for comprehensive studies of the anti-beam properties of chemical radioprotectors. The aim of the study is to study the effect of the RS-10 radioprotector on protein-steroid interaction in irradiated guinea pigs with biphasic adrenocortical response to irradiation. Study methods: experiments were conducted on 146 guinea pigs weighing 300-350 g, which were exposed to total γ radiation at a dose of 3.5 Gy and 4.5 Gy at a dose rate of 5.76 Gy/min, which caused them radiation disease of II and III severity. Experimental animals were injected intraperitoneally with RS-10 (chitosan bitartrate) 15 minutes before irradiation. Control animals were administered an equal volume of saline. The total plasma content of 11-oxycorticosteroids (11-OKS) was determined by the fluorometric method of Guillemin et al. in the author's modification. The binding capacity of corticosteroid binding globulin (CSG) was determined by gel filtration of De Moor at al. in the author's modification. Conclusions. Prophylactic administration of RS-10 to irradiated animals with a two-phase adreno-cortical reaction to radiation causes a later onset of secondary hypercorticism in the midst of radiation sickness in animals. Prophylactic administration of RS-10 before irradiation reduces the level of free hormone and leads to a decrease in hypercorticism, increasing the reserve capabilities of the binding ability of the CSG at the height of radiation sickness. A leading role in the mechanism of reducing affected hypercorticism under protective conditions has a lesser degree of impairment of the binding capacity of the CSG, rather than a change in the total level of 11-OKS in the blood.

Keywords— Radioprotectors, Protein-Steroid Interaction, Corticosteroids, Radiation Sickness, RS-10.

1. INTRODUCTION

Currently, there is an increase in threats to the radiation safety of the population, which makes it urgent to conduct comprehensive studies of the anti-radiation properties of chemical radioprotectors. Questions about the effect of chemical radioprotectors on the radioresistance of the body are relevant in radiobiology and medicine [1-4]. In modern Russian radiobiology, radiobiological concepts, classifications and pharmacological mechanisms of action of anti-radiation agents are presented [5-8]. The problems of radioprotective properties of radioprotectors are also reflected in foreign studies [9, 10]. The

radioresistant properties and mechanisms of the anti-radiation action of the RS-10 radioprotector are described [11].

Currently, radioprotectors are widely used in medical practice in the treatment of cancer patients [12-14]. Clinical studies have shown the effectiveness of using radioprotectors in the radiotherapy of cancer patients to reduce both acute and distant radiation lesions of healthy tissues [15, 16]. The use of radioprotectors in medical practice provides an increase in the degree of tolerability of radiation therapy by cancer patients [17-19].

It was found that various antiradiation agents, in addition to stimulating the hypothalamus-pituitary-adrenal cortex system, could prevent with prophylactic administration development of a secondary reaction of the adrenal cortex in radiation sickness [5-7]. The adrenocortical reaction to radiation in almost all animal species has a two-phase curve. Secondary hypercorticism after a decrease in the total level of corticosteroids in the blood was not detected only in rabbits [20]. In this regard, it is important to study the role of binding of corticosteroids to plasma proteins in the mechanism of the effect of the radioprotector RS-10 on the function of the adrenal cortex in irradiated animals with a two-phase curve on irradiation. The aim of the study was to study the effect of the radioprotector PC10 in radioprotective doses on the level of free corticosteroids in the blood of irradiated animals, as well as the binding ability of the cotricosteroid-binding globulin (transcortin) of blood plasma.

2. METHODS

The generalization of the results of experiments aimed at assessing the effectiveness of the RS-10 radioprotector was carried out on the basis of the Peoples' Friendship University of Russia (RUDN), Moscow in March-April 2023. The research protocol was discussed and approved at a meeting of the Ethics Committee of the RUDN Medical Institute dated March 16, 2023. Animal experiments were previously conducted behind closed doors at the FSBI SSC FMBC named after A.I. Burnazyan FMBA of Russia, which did not allow their results to be presented in open scientific sources.

Reaction of the pituitary-adrenal system and the binding processes of 11-OCS to plasma proteins after irradiation under the protection of RS-10 were investigated in guinea pigs with a biphasic change in the total level of 11-OCS in the dynamics of radiation sickness. The experiment involved 146 guinea pigs weighing 300-350 g. All the animals were preliminarily adapted to the experimental conditions. The guinea pigs were totally irradiated with y-rays at the dose of 3,5 Gy and 4,5 Gy at the dose rate of 5,76 Gy /min, which caused them to have radiation sickness of II and III severity. RS-10 (chitosan bitartrate) was administered intravenously 15 min before irradiation. Control animals were injected with an equal volume of saline. The total content of 11-oxycorticosteroids (11-OCS) in blood plasma was determined by the fluorometric method by Guillemin et al. in the author's modification. The amount of free corticosteroids was determined by the difference in their content in whole plasma and in its protein fraction after separation on Sephadex G-25. The binding capacity of CBG was determined by gel filtration by De Moor et al. in the author's modification [20].

For irradiated guinea pigs protected by RS-10, the parameters of 11-OCS secretion and binding to blood plasma proteins were determined after irradiation at the doses of 3,5 Gy and 4,5 Gy. The total content of 11-OCS was determined before and after 2.5-3 hours and in 1, 3, 7, 14, and 21 days after irradiation at the dose of 3,5 Gy and 4,5 Gy. In addition, for animals irradiated at the dose 4,5 Gy, on the 7th day of radiation sickness with prophylactic administration of RS-10, the fractional composition was determined (total level, free hormone, and the binding capacity of CBG).

Statistical analysis of the results of the study was carried out using the Student-Fisher method. The differences were significant at p 0.05 and less.

3. RESULTS

The results obtained reflect the general level of 11-OCS in the dynamics of radiation sickness in protected and control guinea pigs irradiated at 3,5 Gy (Figure 1).

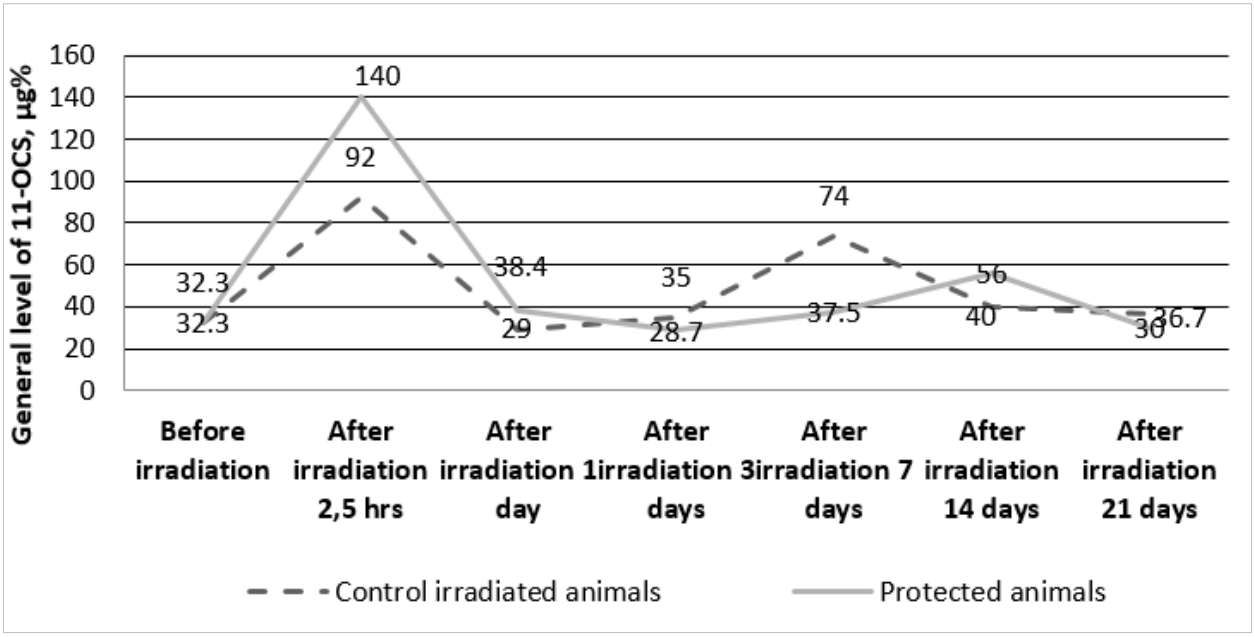

Fig. 1. The general level of 11-OCS in protected and control irradiated guinea pigs in the dynamics of radiation sickness (dose 3,5 Gy).

In the dynamics of radiation sickness, prophylactic administration of RS-10 before irradiation led to a greater increase in the total content of 11-OCS in the blood than in control animals (140 ± 10.5 µg%). After 24 hours, the total blood level of 11-OCS in the control and protected animals decreased to normal (29.0 ± 3.2 and 38.4 ± 3.0 µg%, respectively), remaining at the same level on Day 3 of radiation sickness (35.0 + 2.8 and 28.7 ± 4.3 µg%, respectively).

On the 7th day, for the control guinea pigs it was observed a secondary increase in the total level of 11-OCS to 74.0 ± 6.9 µg%, while in the protected ones it remained normal (37.5 ± 2.9 µg%). On the 14th day of radiation sickness, the total content of 11-OCS in the control animals decreased to the initial level, while in the protected animals there was a secondary increase to 56.0 ± 4.0 µg%. On the 21st day after irradiation, the total content of 11-OCS in both control and protected guinea pigs with RS-10 was within the normal range.

The results obtained at the next stage of the experiment reflect the general level of 11-OCS in the dynamics of radiation sickness in protected and control guinea pigs irradiated at 4,5 Gy (Figure 2).

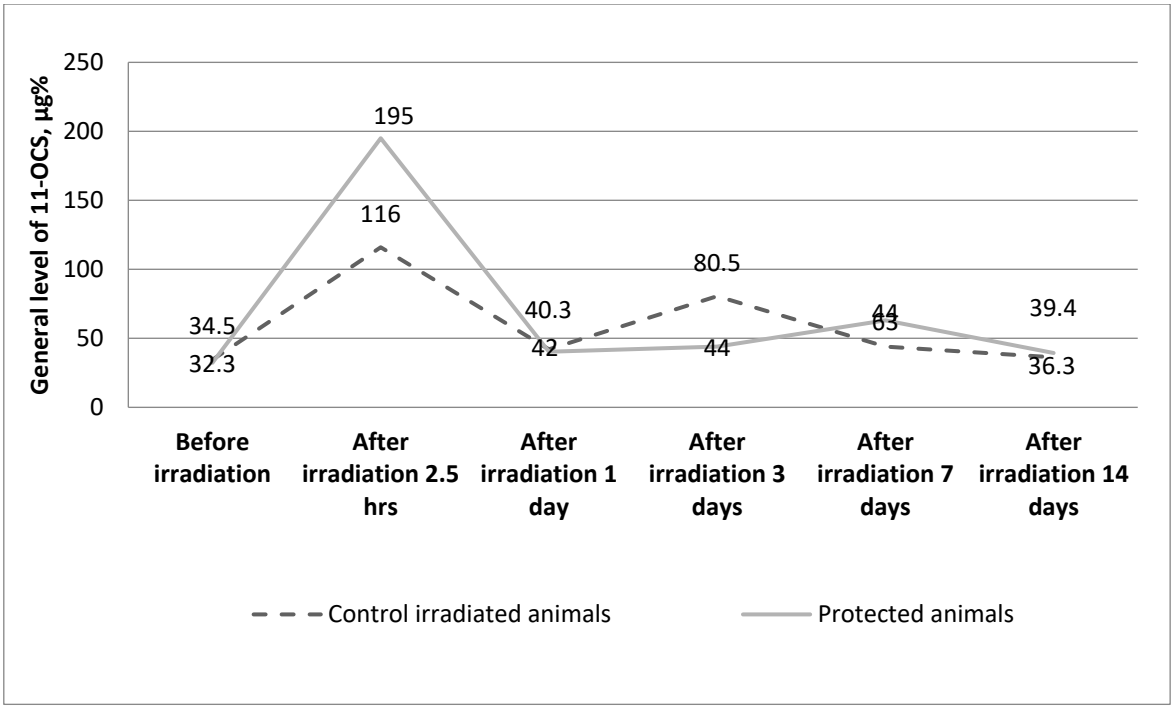

Fig. 2. The general level of 11-OCS in protected and control irradiated guinea pigs in the dynamics of radiation sickness (dose 4,5 Gy).

The results showed that an increase in the radiation dose did not change the nature of the adrenocortical reaction in control and protected guinea pigs, causing only increase of its quantitative level and time parameters. Thus, a repeated rise in the total content of 11-OCS in the blood at the height of radiation sickness was observed in control animals on the 3rd day (80.5 ± 7.2 µg%) after irradiation, and in protected animals on the 7th day (63.0 ± 4.0 µg%), but its normalization occurred on the 7th and 14th day, respectively.

On the 7th day of radiation sickness, the determination of the fractional composition of 11-OCS showed that in the protected guinea pigs (against the background of a higher total level of corticosteroids than in the control group) the free hormone was significantly lower than in the control group (15.0 ± 2.1 µg% and 26.0 + 2.7 µg%, respectively); and the bound hormone was significantly higher (48.0 ± 3.1 µg% and 18.0 ± 3.0 µg%, respectively). The proportion of free hormone in guinea pigs not receiving RS-10 was 59%, and in protected ones only 24% (Figure 3).

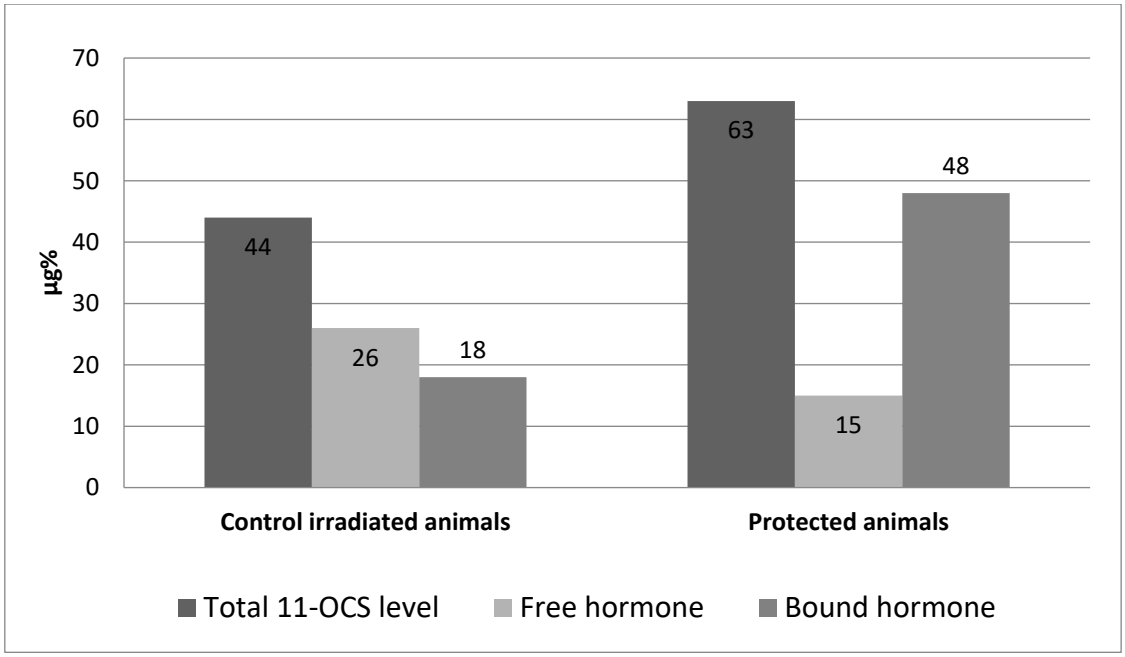

Fig. 3. Influence of prophylactic administration of RS-10 on the fractional composition of 11-OCS in guinea pigs irradiated at 4,5 Gy on the 7th day of radiation sickness.

Thus, prophylactic administration of RS-10 to guinea pigs before irradiation at 3,5 Gy and 4,5 Gy caused a more pronounced early reaction of the pituitary-adrenal system and delayed the onset of secondary hypercortisolism. However, even with a high content of 11-OCS in the blood in such animals, most of those were in an inactive state associated with protein, and the level of the free fraction was significantly lower than in control animals.

4. DISCUSSION

Prophylactic administration of RS-10 causes a later onset of secondary hypercortisolism at the height of radiation sickness in animals with a biphasic adrenocortical reaction to irradiation. In the midst of radiation sickness, in protected guinea pigs the secondary corticoid peak occurs at a later date on Days 14 and 7, while in control animals it was noted on Days 7 and 3, respectively. The data obtained clarify the existing ideas about the effect of the RS-10 radioprotector on the adrenal cortex secondary reaction. According to the general level of 11-OCS, RS-10 does not prevent this reaction but postpones its onset, which, apparently, is associated with a decreased severity of radiation damage under the influence of the protector, since it is known that with a decrease in the radiation dose, the secondary reaction is postponed. In the midst of radiation sickness, prophylactic administration of RS-10 inhibits a decrease in the CBG binding capacity, and, as a result, an increase in the level of free hormone. Against the background of an increase in the binding capacity of the CBG, a secondary increase in the total level of 11-OCS does not lead to an increase in the free fraction of the hormone, since the binding capacity of the CBG exceeds the total level of 11-OCS. In the mechanism of reducing post-radiation hypercortisolism when protected with PS-10, the key factor is a lower degree of CBG binding capacity disorder rather than a change in the total level of 11-OCS in the blood.

The radioprotective efficacy of the drug RS-10 is presented in experiments on dogs [21]. However, studies on dogs were conducted without taking into account the effect of the RS-10 radioprotector on the interaction of corticosteroids with plasma proteins. A number of studies present the results of trials of the

drug RS-10 as an anti-radiation agent in the early stages of acute radiation sickness [22]. The preventive properties of RS-10 are shown in the studies of Rozhdestvensky [7]. The anti-radiation effect of RS-10, according to Rozhdestvensky, shows similarity in the nature of the anti-radiation effect with cytokines and lipopolysaccharides and is effective when administered both before and after irradiation. In fact, by its effects, PC-10 is a hybrid drug integrating the properties of oxidomodulators and cytomodulators [7]. These provisions are also confirmed by our studies, which allow us to consider PC-10 as an effective anti-radiation agent for the prevention of radiation sickness. The analysis of the anti-radiation characteristics of RS-10 allows us to evaluate its pharmacological properties in a new way from the point of view of the prevention of radiation sickness. The damaging effect of radiation is largely prevented by the preliminary introduction of the RS-10 radioprotector.

5. Conclusions

1. Prophylactic administration of PC10 to irradiated animals with a two-phase adrenocortical reaction to irradiation causes a later onset of secondary hypercorticism in the midst of radiation sickness in animals.

2. Prophylactic administration of PC10 before irradiation reduces the level of free hormone and leads to a decrease in hypercorticism, increasing the reserve capacity of the binding ability of CSG in the midst of radiation sickness.

3. The leading role in the mechanism of reducing radiation hypercorticism under protective conditions is played by a lesser degree of violation of the binding ability of CSG, and not by a change in the overall level of 11-ACS in the blood.

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