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Significance of corticosteroids binding to blood plasma proteins in the mechanism of the RS-10 radioprotector affecting the function of the adrenal cortex

Importancia de la unión de corticosteroides a proteínas del plasma sanguíneo en el mecanismo del radioprotector RS-10 que afecta la función de la corteza suprarrenal

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SUMMARY

The relevance of research on the preventive properties of chemical radioprotectors is currently due to the need to implement a system of radiation safety measures for the population. The study aimed to investigate the significance of corticosteroid binding to plasma proteins in the mechanism of influence of the radioprotector RS-10 on adrenal cortical function in healthy and irradiated animals. Experiments were carried out on 60 male rabbits of the chinchilla breed. In the first series of experiments, the reaction of the adrenal cortex and the processes of binding them to proteins after administration of RS-10 intact animals were studied; in the second series - the same indicators in animals exposed to RS-10 prophylactic administration. Rabbits were irradiated totally with 8 Gy rays. RS-10 (chitosan bitartrate) was administered intravenously at 10.0 mg/kg 15 minutes before irradiation. The control animals were administered an equivalent volume of saline. In the dynamics of radiation sickness in protected RS-10 rabbits, a significantly lower decrease in the binding ability of corticosteroid-binding globulin (CSG) was observed than in control animals. Prophylactic administration of RS-10 before irradiation reduces the free hormone level and, as a result, leads to a decrease in hypercorticism, increasing the reserve capabilities of the binding ability of the CSG at the height of radiation sickness.

Keywords: *Radioprotectors, protein-steroid interaction, corticosteroids, radiation sickness, RS-10.*

RESUMEN

La relevancia de la investigación sobre las propiedades preventivas de los radioprotectores químicos se debe actualmente a la necesidad de implementar un sistema de medidas de seguridad radiológica para la población. El objetivo del estudio es investigar la importancia de la unión de corticosteroides a proteínas plasmáticas en el mecanismo de acción del radioprotector RS-10 sobre la función cortical suprarrenal en animales sanos e irradiados. Los experimentos se llevaron a cabo en 60 conejos machos de la raza chinchilla. En la primera serie de experimentos, se estudió la reacción de la corteza suprarrenal y los procesos de unión a proteínas después de la administración a animales intactos RS-10; en la segunda serie, los mismos

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indicadores en animales expuestos a la administración profiláctica de RS-10. Los conejos se irradiaron totalmente con rayos de 8 Gy. Se administró RS-10 (bitartrato de quitosano) por vía intravenosa 10.0 mg / kg 15 minutos antes de la irradiación. A los animales control se les administró un volumen equivalente de solución salina. En la dinámica de la enfermedad por radiación en conejos RS-10 protegidos, se observó una disminución significativamente menor en la capacidad de unión de la globulina que se une al corticoide (CSG) que en los animales de control. La administración profiláctica de RS-10 antes de la irradiación reduce el nivel de hormona libre y, como resultado, conduce a una disminución del hipercorticismo, aumentando las capacidades de reserva de la capacidad de unión del CSG a la altura de la enfermedad por radiación.

Palabras clave: *Radioprotectores, interacción proteína-esteroide, corticosteroides, enfermedad por radiación, RS-10.*

INTRODUCTION

Currently, threats to the radiation safety of the population are increasing. The need to conduct comprehensive studies of the anti-beam properties of chemical radioprotectors is urgent. These studies should be carried out from the standpoint of a systematic approach since the body responds to radiation exposure with a complex of pathological reactions of various levels and systems (1,2). An important link in the pathogenesis of acute radiation syndrome is the pituitary-adrenal system. A comprehensive analysis of changes in the functional state of the adrenal cortex in radiation damage and in conditions of increased resistance makes it possible to determine its role in the development and outcome of radiation sickness, in the processes of restoration of radiosensitive tissues (2). The achievements of modern science have made it possible to create a solid theoretical basis for controlling tissue radiosensitivity to increase the effectiveness of radiation sickness therapy (3). Nowadays, various classifications of anti-beam agents have been developed in radiobiology, and the mechanisms of their protective action have been described. Scientific publications of Russian (4-7) and foreign researchers (8,9) are devoted to these problems.

The issues of clinical studies of the effectiveness of radioprotectors in radiation therapy of cancer patients remain relevant. Radioprotectors are widely used in radiation therapy of malignant tumors to reduce acute and distant radiation lesions of healthy tissues and increase the tolerance of radiation therapy by cancer patients (10-12).

The scientific interest of researchers is attracted by the questions of radioresistant properties and mechanisms of the anti-beam action of the RS-10 radioprotector (13-15). One of the mechanisms of action of chemical radioprotectors that increase the radioresistance of the body is the change in the affected reaction of the pituitary-adrenocortical system (16). Questions about the effect of the radioprotector RS-10 on the binding of corticosteroids to plasma proteins in intact and irradiated animals when administered prophylactically are noteworthy.

The study aims to investigate the significance of corticosteroid binding to plasma proteins in the mechanism of influence of the radioprotector RS-10 on adrenal cortical function in healthy and irradiated animals.

MATERIALS AND METHODS

This experimental study aimed to investigate the significance of corticosteroid binding to plasma proteins in the mechanism of influence of the radioprotector RS-10 on adrenal cortical function in healthy and irradiated animals. It was carried out based on 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 Burnazyan FMBA of Russia, which did not allow their results to be presented in open scientific sources.

Studies were carried out on 60 male rabbits of the chinchilla breed weighing 2.5-3.0 kg. Two series of studies were conducted. In the first series, the reaction of the adrenal cortex and the processes of binding them to plasma proteins after administration of PC-10 to intact animals were studied; the second series focused on the same indicators in irradiated animals with prophylactic administration of RS-10. All the animals were

preliminarily adapted to the experimental conditions. Rabbits were irradiated totally with U-rays at a dose of 8 Gy, causing acute stage IV radiation sickness. RS-10 (chitosan bitartrate) was administered intravenously at the rate of 10.0 mg/kg 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 calculated by the difference in their content in whole plasma and in its protein fraction after separation on Sephadex G-25. The binding capacity of corticosteroid binding globulin (CBG) was determined by gel filtration by De Moor et al. with authors' modification (17). CBG is a well-characterized glycoprotein capable of binding adrenal steroid hormones. Plasma corticosteroid-binding globulin originates mostly from the liver and regulates the systemic bioavailability of glucocorticoids and mineralocorticoids.

In intact rabbits, the total content of 11-OCS was determined before and after 1, 2, 3, 6, and 24 hours after administration of RS-10. Free and protein-bound 11-OCS and the binding capacity of CBG were determined before and after 2.5-3 hours (at the time of the maximum rise in the total 11-OCS level) after administration of RS-10. In irradiated animals protected by RS-10, the total content of 11-OCS was determined before and after 2.5-3 hours, on the 4^{th}, 8^{th}, 14^{th}, 21^{st}, and 30^{th} days after irradiation. In addition, after 2.5-3 hours, on the 4^{th} and 8^{th} days, free 11-OCS, and the binding capacity of CBG were determined.

Statistical analysis of the study results was performed using the Student-Fisher method. Differences at $p < 0.05$ and less were considered significant.

RESULTS

The dynamics of changes in the total concentration of 11-OCS in the blood plasma of intact rabbits after administration of RS-10 showed an increase in the total content of 11-OCS in the blood after 1, 2, and 3 hours with the maximum after 2.5-3 hours; it remained significantly higher than the initial level after 6 hours. On the first day, the total level of 11-OCS in the blood was normalized (Table 1).

Table 1. Dynamics of changes in the total concentration of 11-OCS in the blood plasma of Intact rabbits after administration of RS-10 and saline

A group of rabbits	Indicators	Before administration, μg/100 mL	Time after RS-10, hours 1 hour	2 hour	3 hour	6 hour	24 hour
Experiment (administration of the RS-10)	M, m	7.4 ± 0.6	14.2 ± 0,5	18.7 ± 2.1	17.9 ± 0.6	11.6 ± 0,8	7.3 ± 0.5
	n	10	10	10	10	10	10
	*P		<0.001	< 0.001	< 0.001	< 0.01	> 0.05
Control (administration of saline)	M, m	7.5 ± 0.4	7.45 ± 0,3	7.0 ± 0,2	7.25 ± 0,4	6.7 ± 0,3	7.3 ± 0,2
	n	4	4	4	4	4	4
	*p	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	
	**p		<0.001	< 0.001	< 0.001	< 0.01	> 0.05

*p is the level of significance of differences between the corresponding indicators in animals of each group in comparison with the initial value. **p is the same in irradiated control rabbits and rabbits protected with RS-10.

It should be noted that in 20 % of rabbits, in which the initial level of the hormone exceeded the average normal value, amounting to 10.0 and 11.5 μg/100 mL, respectively, the administration of RS-10 caused a weaker increase in the total content of 11-OCS (by about 35 %) and a less prolonged reaction of the adrenal cortex. In the remaining 80% of rabbits (in which the initial

total content of 11-OCS was 5-7 μg/100 mL) the administration of RS-10 caused a sharp and more prolonged increase in the function of the adrenal cortex when the total content of 11-OCS increased by 2-2.5 times. This is consistent with the data on the stimulatory effect of polysaccharides on the pituitary gland, which is regulated by preexisting levels of circulating glucocorticoids.

The study of the fractional composition showed that the total content of 11-OCS in intact rabbits after 2.5-3 hours (at the moment of the maximum severity of the reaction) after administration of RS-10 increased from 7.9 ± 0.6 to 19.2 ± 1.0 μg/100 mL (*p <0.001) (Table 2).

Table 2. The total level and the amount of free 11-OCS, and the binding capacity of CBG in the blood plasma of rabbits in normal conditions and 2.5-3 hours after administration of RS-10

Rabbits	Indicators	The total level of 11-OCS, μg/100 mL	Free 11-OCS μg/100 mL	%	Bound 11-OCS μg/100 mL	The binding capacity of CBG, μg/100 mL
		Before administering RS-10				
Control (administration of saline)	M, m n	8.7 ± 1.0 3	0	0	8.7 ± 1.0 3	13.8 ± 1.0 3
Experiment (administration of the RS-10)	M, m n	7.9 ± 0.6 7	0.2 ± 0.05	0	7.7 ± 0.6 7	12.5 ± 0.6 7
		After administering RS-10				
Control (administration of saline)	M, m n *p	9.5 ± 0.7 3 >0.05	0.3 ± 0.1 >0.05	0	9.2 ± 0.8 3 >0.05	12.7 ± 0.8 3 >0.05
Experiment (administration of the RS-10)	M, m n *p **p	19.2 ± 1.0 7 <0.001 <0.001	6.2 ± 0.9 7 <0.001 <0.001	32	13 ± 0.8 7 <0.001 <0.001	11.8 ± 0.7 7 >0.05 >0.05

Note: *p is the level of significance of differences between the corresponding indicators in animals of each group in comparison with the initial value. **p is the same in irradiated control rabbits and rabbits protected with RS-10

The level of free corticosteroids reached 6.2 ± 0.9 μg/100 mL, which was 32 % of the total amount of 11-OCS, while in normal rabbits, free corticosteroids are practically absent. The content of plasma protein-bound 11-OCS significantly increased from 7.7 ± 0.6 to 13.0 ± 0.8 μg/100 mL (*p <0.001). The binding capacity of CBG after the introduction of RS-10 did not change. The administration of saline did not change either the concentration of corticosteroids or the binding capacity of CBG.

Prophylactic administration of RS-10 makes the reaction of the adrenal cortex in rabbits 2.5-3 h after irradiation more pronounced than in control animals (**p < 0.01) (Table 3).

This is evidenced by a more pronounced increase in the content of total (14.8 ± 0.9 and 11.0 ± 0.8 μg/100 mL, *p < 0.01) and free (4.0 ± 0.8 and 1.8 ± 0.5 μg/100 mL, *p < 0,05) 11-OCS, respectively, in protected and control irradiated rabbits. In this case, the amount of free 11-OCS in the irradiated control was 15 %, and in the protected irradiated rabbits, 25 % of the total amount of 11-OCS in the blood. The binding capacity of CBG in both groups of

Table 3. Influence of prophylactic administration of RS-10 on the total level of 11-OCS in irradiated rabbits

A group of rabbits	Indicators	Before irradiation, μg/100 mL	Time after irradiation 2.5 hours	4 days	8 days	14 days	21 days	30 days
Irradiated control	M, m	7.3 ± 0.9	11.0 ± 0.8	5.1 ± 0.4	4.1 ± 0.3	4.2 ± 0.7	5.3 ± 0.5	6.7 ± 0.5
	n	17	16	15	12	7	6	6
	P*		<0.01	<0.05	<0.01	<0.02	>0.05	>0.05
Protected with RS-10	M, m	7.5 ± 0.5	14.8 ± 0.9	6.7 ± 0.5	6.2 ± 0.9	4.7 ± 1.2	6.0 ± 0.6	7.7 ± 0.7
	n	25	25	16	8	7	10	13
	*p		< 0.05	>0.05	>0.05	>0.05	>0.05	>0.05
	**p		< 0.01	< 0.05	< 0.05	>0.05	>0.05	>0.05

Note: *p is the level of significant differences between the indices in animals of each group before and after irradiation; **p is the same in control animals irradiated and protected with RS-10.

animals did not change. The appearance of a free fraction of corticosteroids in the first hours after irradiation in control animals and animals protected with RS-10, as well as in intact rabbits after administration of RS-10, is due only to an increase in the total level of hormones, which is a typical reaction for a nonspecific stress state.

In the late period of radiation sickness (on the 4th, 8th, and 14th days), the total content of 11-OCS in control rabbits decreased and was, respectively, 5.1 ± 0.4 μg/100 mL (*p < 0.05), 4.1 ± 0.3 μg/100 mL (*P < 0.05) and 4.2 ± 0.7 μg/100 mL (*P < 0.02). On the 21st and 30th days, it returned to the initial one, amounting to 5.3 ± 0.5 and 6.7 ± 0.5 μg/100 mL. Before and after this period, it fluctuated within the original values. In protected rabbits on days 4 and 8, the total hormone content was 6.7 ± 0.5 μg/100 mL and 6.2 ± 0.9 μg/100 mL and was significantly higher than in control animals, in which these indicators had a level of 5,1 ± 0.4 and 4.1 ± 0.3 μg/100 mL (**p < 0.05). Some of the irradiated rabbits, both controlled and protected, died. The rest of the animals remained alive during the entire observation period, that is, over 30 days.

To assess the role of the functional state of the adrenal cortex in the outcome of radiation sickness, the changes in the total level of 11-OCS in the blood were examined separately in dead and surviving animals (Figure 1).

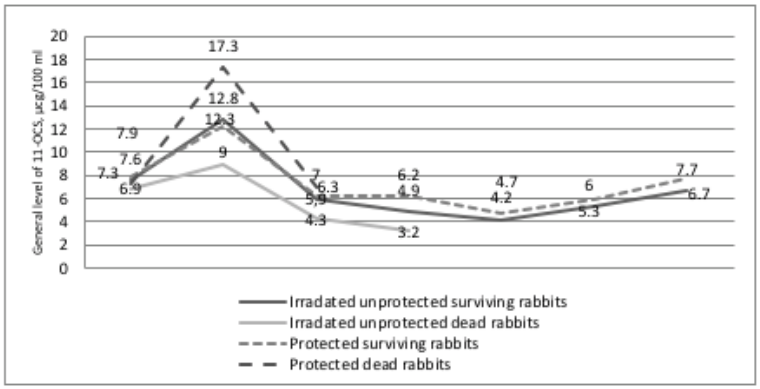

Figure 1. Dynamics of changes in the total level of 11-OCS in irradiated and protected rabbits, depending on the outcome of radiation sickness. *p, *p1 is the level of significance of differences between the indicators in animals in each group before and after irradiation; **p, **p1 - the same for dead and surviving in each group.

The shifts in the adrenocortical reaction in all the studied animals were the same type, but their severity was different. In protected animals, the reaction of the pituitary-adrenal system in the first hours after irradiation was more pronounced in the dead than in the surviving animals (17.3 ± 1.3 and 12.3 ± 0.7 μg/100 mL, respectively, **p1 < 0.01). In animals irradiated without protection, on the contrary, the reaction of the adrenal cortex in the survivors was more pronounced than in the dead (12.8 ± 1.4 and 9.0 ± 0.4 μg/100 mL, respectively, **p < 0.05). In the control rabbits that died at the height of radiation sickness, the total content of 11-OCS was always significantly lower than in the survivors, both not receiving and receiving RS-10 (*p 1 < 0.01, *p < 0.05).

Notably, the level of 11-OCS after irradiation in surviving animals (both protected and control) was almost the same at all stages of radiation sickness (Figure 1). In all the dead rabbits, the reaction of the adrenal cortex in the first hours after irradiation was either weaker or much stronger than in the surviving ones. The severity of the primary reaction of the adrenal cortex, apparently, is associated with the mechanisms that determine radioresistance. The same increase in the total hormone level in surviving animals (both protected and control) may indicate that the mechanisms of physiological and chemical protection are developing on a common basis. The reaction of the adrenal cortex in surviving animals without protection was an indicator of the 'optimal' level of the hormone. The sharp increase in the total content of corticosteroids in the blood of rabbits that died in the early period after administration of RS-10 and irradiation is probably associated with the terminal period of radiation sickness when the concentration of 11-OCS in the blood increases. Evaluating the functional state of the adrenal cortex in the late stages of radiation sickness reveals that the administration of RS-10 promotes the preservation of the pituitary-adrenal system activity.

Investigation of corticosteroid-protein interaction in control and protected rabbits showed that an increase in the level of total and free 11-OCS in the blood in the first 2.5-3 hours after irradiation is not accompanied by a change in the binding capacity of CBG (12.3 ± 0.8 μcg/100 ml and 11.9 ± 0.9 μg/100 mL, respectively) (Table 4).

Table 4. Change in the total level of free 11-OCS and the binding capacity of CBG in protected and control irradiated rabbits

Group of rabbits	Indicators	Before irradiation	After irradiation												
			2.5 hours				4th day				8th day				
		BC of CBG (μg/100 mL)	BC of CBG (μg/100 mL)	TL (μg/100 mL)	FH (μg/100 mL)	%	BC of CBG (μg/100 mL)	TL (μg/100 mL)	FH μg %	%	BC of CBG (μg/100 mL)	TL (μg/100 mL)	FH (μg/100 mL)	%
Protected by RS-10	M, m	12.9± 0.6	12.3± 0.8	15.6± 1.3	4.0± 0.8	25	8.3± 0.8	8.0± 0.8	0.8± 0.2	10	9.6± 0.2	8.2± 0.7	Practically absent	4
	n	10	10	10	10		8	8	8		7	7		
	*p		> 0.05				> 0.001				> 0.001			
Control irradiated	M, m	13.1± 0.8	11.9± 0.9	12.2± 1.0	1.8± 0.5	15	3.8± 0.5	5.8± 0.6	2.3± 0.3	39 0.6	5.0± 0.4	4.5± 0.2	0.6±	13
	n	8	8	8	8		6	6	6		5	5	5	
	*p						< 0.01				< 0.01			
	**p		> 0.05	< 0.05	< 0.05		< 0.001	< 0.05	< 0.02		< 0.01	< 0.001		

Note: BC of CBG – binding capacity of CBG (μg %); TL – total level (μg %); FH – free hormone; *P is the level of reliability of differences between indicators in animals of each group before and after irradiation; **p – the same in control irradiated and protected animals.

Later, on the 4th and 8th days of radiation sickness, the binding capacity of CBG decreased both in the control and in the experiment group of animals (*p < 0,001). However, in protected rabbits, it was significantly higher than in the irradiated control. Irradiation with the administration of RS-10 after 2.5-3 hours led to a greater increase in the total level of the hormone than in the control (**p < 0.05).

Thus, the formation of the free fraction of the hormone in intact rabbits treated with RS-10, as well as in those irradiated with its prophylactic administration, in the first hours after exposure is due to an increase in the total level of corticosteroids in the blood, since the binding capacity of CBG did not change.

At the same time, at a later time after irradiation, significant differences were found in the protected and control animals in the interaction of the protein with corticosteroids. On the 4th day after irradiation, the control rabbits showed a significant increase in free corticosteroids up to 2.3 ± 0.3 μg/100 mL (39 % of the total hormone content) against the background of a reduced total level of corticosteroids in the blood (5.8 ± 0.6 μg/100 mL) and a sharp decrease in the binding capacity of CBG in blood plasma to 3.8 ± 0.5 μg/100 mL (*p < 0.001). It should be emphasized that the total concentration of 11-OCS exceeded the binding capacity of CBG.

A different picture was observed in the irradiated animals protected by RS-10. The total content of 11-OCS was significantly higher than in the control animals – 8.0 ± 0.8 μg/100 mL and 5.8 ± 0.6 μg/100 mL (**p < 0.05). Although the binding capacity of CBG in protected animals was reduced; it was more than twice as high in control irradiated rabbits – 8.3 ± 0.8 μg/100 mL and 3.8 ± 0.5 μg/100 mL (**p<0.001). As a result of this relationship between the total concentration of 11-OCS and the binding capacity of CBG in protected irradiated rabbits, the amount of free hormone decreased to 0.8 ± 0.2 μg/100 mL at 2.3 ± 0.3 μg/100 mL in control (**p< 0.05). Fundamentally similar data were noted on the 8th day after irradiation.

Thus, on the 4th day after irradiation in protected animals, despite the higher total level of the hormone, the content of its free fraction (due to the higher binding capacity of the CBG) was lower than in the control irradiated animals. On the 8th day after irradiation, in both the control irradiated and protected animals the free fraction of 11-OCS was practically absent. The total level of 11-OCS in protected animals exceeded that in control animals, amounting to 8.2 ± 0.7 μg/100 mL and 4.5 ± 0.4 μg/100 mL; **p < 0.001, respectively. At the same time, in the control rabbits, the binding capacity of CBG was low (5.0 ± 0.6 μcg/100 mL), and in those irradiated after administration of RS-10, the binding capacity of CBG was higher than in the control (*P* < 0.01), although it did not reach the initial value, amounting to 9.6 ± 0.2 μg/100 mL.

DISCUSSION

The results of the study made it possible to reveal the preventive effect of the radioprotector PC-10 in the context of its effect on the function of the adrenal cortex in healthy and irradiated animals, namely, changes in the binding of corticosteroids to blood plasma proteins. It should be noted that a number of studies are devoted to the preventive properties of PC-10. A high preventive of RS-10 is shown the works of Rozhdestvensky (3,15). However, the author also notes the toxicity of RS-10 to humans (6,15). The high preventive efficacy of the drug RS-10 is shown in experiments on dogs (13). However, in experiments in dogs, there is no analysis of the effect of the radioprotector RS-10 on the protein-steroid interaction of blood plasma of irradiated animals. Other papers present the results of testing the drug RS-10 as an anti-radiation agent in the early stages of acute radiation sickness (14). These studies were carried out without taking into account the effect of the PC-10 protector on the protein-steroid interaction in irradiated and healthy animals.

The advantage of this study is that for the first time, the findings made it possible to describe the prophylactic properties of the radioprotector PC-10 by analyzing its effect on the binding of corticosteroids to blood plasma proteins in irradiated and healthy animals. In the dynamics of radiation sickness in protected RS-10 rabbits, a significantly lower decrease in the binding ability of corticosteroid-binding globulin (CSG) was observed than in control animals. At the height

of radiation sickness on day 4 after irradiation, the total 11-OCS content in protected RS-10 rabbits was higher than in the control, and the level of free hormone was sharply reduced. On the 8th day of radiation sickness, there were practically no free 11-OCS in protected RS-10 and control rabbits, however, in protected animals, the binding ability of CSG was higher than in unprotected (control) animals, in which any stressful effects against the background of reduced binding ability of CSG could lead to the appearance of significant amounts of free 11-OCS.

Prophylactic administration of RS-10 before irradiation reduces the free hormone level and, as a result, leads to a decrease in hypercorticism, increasing the reserve capabilities of the binding ability of the CSG at the height of radiation sickness. Prophylactic administration of the radioprotector RS-10 stimulates, in the first hours after irradiation, corticoid hypersecretion to a level exceeding the plasma binding capacity of the hormone. Thus, an increase in the early, protective reaction of the adrenal cortex and its approach to the optimal is achieved. This confirms the high preventive effectiveness of the drug RS-10. The conclusions of the experiments make it possible to consider RS-10 as an effective anti-radiation agent for the treatment and prevention of acute radiation disease.

CONCLUSIONS

1. One of the mechanisms of the radioprotective effect of the RS-10 radioprotector is to establish the optimal response of the adrenal cortex in the first hours after irradiation. The difference between the early adrenocortical response in irradiated and protected animals from the optimal one towards both its enhancement and attenuation serves as an indicator of the severity of radiation sickness and a prognostic sign of its outcome.
2. Prophylactic administration of RS-10 before irradiation reduces the free hormone level and, as a result, leads to a decrease in hypercorticism, increasing the reserve capabilities of the binding ability of the CSG at the height of radiation sickness.

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