DEPRESSION OF THE FUNCTIONING OF THE PHYSIOLOGICAL ANTICOAGULATORY SYSTEM IN EXPERIMENTAL RADIATION SICKNESS OF ANIMALS

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In the experiments of B. A. Kudryashov and P. D. Ulitina [3, 4], the first proof was given of the presence in the animal organism of a physiological anticoagulatory system (ACS), whose function consisted of the secretion of a number of humoral agents into the blood stream, inhibiting blood coagulation, in response to the intravenous injection of thrombin or thromboplastin. The functioning of the ACS was accomplished by means of neuro-humoral mechanisms [5, 6].

It was shown that, in animals, the functioning of the ACS is suppressed by deep, general ether narcosis. In this case, the injection of thrombin or thromboplastin caused the death of the experimental animals from advancing thrombosis of the vessels, while the control animals remained alive. Intramuscular injection of significant doses of novocain also caused suppression of the ACS, and in a considerable number of the cases, was accompanied by death of the animals [3].

Keeping animals on Vil'gram's atherogenic diet for 3-5 months led to depression of the ACS, manifested by lowering of the fibrinolytic activity of the blood, an increase in the concentration of fibrinogen, and a rise in the tolerance of the plasma to heparin. Spontaneous thromboses occurred in the heart and vessels of the animals. Fatal thrombus formation was easily provoked in these animals by the intravenous injection of moderate doses of thrombin [7].

Blockade of the reticulo-endothelial system, accomplished by injection of the healthy animals with trypan blue, also led to partial suppression of the ACS, as reflected in the decreased extent of the reflex humoral reaction to injection of thrombin, and was accompanied by the death of a significant portion of the experimental animals, in contrast to the control group, subsequent to the intravenous injection of thromboplastin [9].

In this work we studied the effect of penetrating radiation on the functioning of the ACS.

It is known that a marked deficiency in prothrombokinase of the blood platelets occurs in irradiated animals, leading to a reduction in the thromboplastic activity of the blood and to a form of hemophilia; capillary strength also decreases substantially [2]. Irradiated animals, with a marked deficiency of prothrombokinase and the presence of hemophilia, can serve as good subjects for the elucidation of ACS functioning in the organism as associated with marked disruption of blood coagulation, accompanied by hemorrhagic diathesis.

EXPERIMENTAL METHOD

Approximately 400 white rats were used in the experiments, weighing 170-190 grams. The animals were irradiated on the RUM-3 apparatus. Conditions of the irradiation: 180 kV, 15 mA, with filter of Cu – 0.5 mm, and Al – 1 mm. During the experiment the animals were maintained on the usual laboratory ration. In both the experimental and control animals the fibrinolytic activity of the blood was determined by the method of Bidwell [10], the tolerance of plasma to heparin according to Gormsen [11], the thromboplastic activity of the blood by the method of Kudryashov and Ulitina [1], the capillary strength by the method of negative pressure, following the modification of I. I. Matusis [8]. For the intravenous injections, we used a physiological saline solution of commercial thrombin preparation, with a 3-4 second activity.

EXPERIMENTAL RESULTS

On the 8-10th day of the trial after irradiation (with a dose of 600 r), the animals showed marked decrease in the thromboplastic activity of their blood and in their capillary strength, as was established earlier (Table 1) [2].

TABLE 1. The Thromboplastic Activity of the Blood and the Capillary Strength in Animals Irradiated with a Dose of 600 r, on the 8-10th Day after Irradiation

Animals	Thromboplastic activity of the blood on the 8-10th day after irradiation (in %)	Capillary strength (in %)	
		Before irradiation	On the 8-10th day after irradiation
Irradiated	24	100	45
Control	95	100	88

On the 8-10th day, the irradiated animals were injected intravenously with moderate doses of thrombin solution (1 ml per 100 grams of body weight). It can be seen from Table 2 that 80% of the irradiated animals died immediately after the injection, in which cases we noted thromboses in the heart and blood vessels. Only a very small number of the control animals died from the administration of the same dose of thrombin. These data indicate that the ACS exists in a depressed state in the irradiated animals, and thromboses of the heart and vessels are easily provoked by the injection of thrombin. Intraveneous injection of an inactivated solution of thrombin (inactivated by heating the solution to 65° for 20-30 minutes) into the irradiated animals did not show any negative effect.

TABLE 2. Survival Rate of Irradiated Animals Following the Intravenous Injection of Thrombin

Animals	Number of animals	Dose of thrombin (in ml)	Animals dying	
			Number	%
Irradiated	40	1.5-1.8	32	80
"	15	1.5-1.8 (inactivated)	–	–
Control	37	1.5-1.8	9	24

It was shown earlier that intravenous injection of thrombin into healthy animals causes a significant elevation in the fibrinolytic activity of the blood [6]. Table 3 shows that the injection of thrombin into both irradiated and normal animals in minimal doses (0.35 ml per 100 grams of body weight) does not lead to the death of the experimental animals, but does not give rise to the reflex defense humoral reaction—elevation of the fibrinolytic activity of the blood. In the control, animals, the fibrinolytic activity increases*.

In both the experimental and control animals we also determined the tolerance of the plasma to heparin, before and after injection of small doses of thrombin (Table 4).

TABLE 3. Fibrinolytic Activity of the Blood of Irradiated Animals Following the Injection of Thrombin

Animals	Number of animals	Dose of thrombin (in ml)	Fibrinolytic activity (in %)	
			Before injection	After injection
Irradiated	27	0.6-0.7	6.5	8.2
Control	27	0.6-0.7	13.2	25

Table 4 shows that the tolerance of the plasma to heparin in the control animals rose considerably at 6-10 minutes after the injection of thrombin. These data correspond with previously published results on the secretion of heparin and heparin-like substances after injection of thrombin into animals [3]. Within an hour after injection of thrombin the plasma tolerance to heparin begins to increase, and returns to normal after 24 h.

In certain irradiated animals (see Table 4, No. 21) the tolerance of the plasma to heparin was close to normal, or somewhat increased; in the larger portion of the animals (No. 1) the plasma tolerance to heparin decreased substantially. This discrepancy is apparently explained by varying stages of the depression of the ACS caused by irradiation.

After injection of the experimental animals with the thrombin, the reflex reaction—decrease in the plasma tolerance to heparin—began later (after an hour) than in the control subjects. Within 6-10 minutes after injection of the thrombin, the maximum reflex reaction appeared in the control animals, and a marked drop in the plasma

*The amount of fibrinogen taken as the "before lysis" figure was determined after a 1 h incubation of the samples, while the "after lysis" figure was determined after 4 hours of incubation at 37°.

tolerance to heparin occurred. In the experimental animals at this time the reaction still appeared to be minimal, and the marked drop in plasma tolerance to heparin began later (after an hour).

TABLE 4. The Tolerance of Plasma to Heparin in Irradiated and Normal Animals Before and After Injection of Thrombin

No.	Animals	Number of animals	Dose of thrombin (in ml)	Plasma tolerance to heparin			
				before injection	after injection		
					after 6-10 minutes	after an hour	after 24 hours
1	Irradiated	25	0.6-0.7	> 30 minutes*	22 minutes 9 seconds	> 30 minutes	16 minutes 50 seconds
2	"	15	0.6-0.7	12 minutes 30 seconds	23 minutes 9 seconds	> 30 minutes	15 minutes 30 seconds
3	Control	37	0.6-0.7	17 minutes 35 seconds	30 minutes	23 minutes 20 seconds	17 minutes 50 seconds

*As a rule, greater than an hour.

The results obtained show that the irradiation of animals with x-rays causes a pronounced weakening and suppression of the ACS. Appearance of thrombin in the vascular bed in a sufficient concentration causes death of the experimental animals in the majority of cases, secondary to advancing thromboses of the vessels, which stands in contrast to the non-irradiated control group. With intravenous injection of small doses of thrombin into irradiated rats, the reflex defense reaction, characterized in the control animals by an elevation of the fibrinolytic activity of the blood, is not observed. In the experimental rats, we also note that the change in the plasma tolerance to heparin in response to intravenous injection of thrombin is more delayed, in comparison with the control animals. The phenomena observed attest to the fact that, after irradiation of animals, the humoral portion of the ACS exists in a depressed state.

SUMMARY

Experiments performed on rats demonstrated X-irradiation of animals (600 r) to depress the physiological anticoagulative system. Intravenous administration of thrombin solution (in sufficiently strong concentration) to the irradiated animals caused immediate death from cardiac vessels and vascular thrombosis; this is distinct from normal animals, which being in the same conditions, remained alive. Intravenous injection of thrombin in low doses failed to cause the death of irradiated animals, nor did it provoke protective reaction of the blood fibrinolytic system, but led to a more gradual change of the plasma tolerance of heparin. In 6-10 minutes after thrombin administration (in the same doses) to control animals there is a rise of the blood fibrinolytic activity and a considerable reduction of plasma tolerance to heparin. The data obtained point to the depression occurring in the humoral part of the physiological anticoagulative system in the irradiated animals.

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