EFFECT OF IONIZING RADIATION ON FUNCTION OF THE VASCULAR AND PLATELET COMPONENTS OF HEMOSTASIS

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Ionizing radiation causes activation of the hemostasis system, intravascular blood clotting, and subsequent development of a thrombohemorrhagic syndrome *in vivo* [5, 7, 9, 10, 14]. Activation of blood clotting in the irradiated animal is observed both in the early period and at the height of radiation sickness, against the background of a bleeding tendency. On the basis of much factual evidence, some workers [2, 4] have attempted to explain the mechanism of this activation of the hemostasis system. However, the effects of ionizing radiation on function of the vascular and platelet (triggering) stages of the hemostasis system and, in particular, on the antiaggregating activity of the vascular wall, still remains an unsolved problem.

The object of this investigation was to study the effect of ^{60}Co γ-rays on the antiaggregating activity of the vessel wall and on aggregating activity of the platelets of rats and guinea pigs, occupying the first and last positions in a series for severity of the hemorrhagic syndrome of acute radiation sickness [6].

EXPERIMENTAL METHOD

Experiments were carried out on 265 Wistar rats weighing 180-240 g and 114 guinea pigs weighing 250-350 g. Acute radiation sickness was induced by irradiating the animals on a "Gammacell-220" apparatus (dose rate 0.16-0.17 Gy/sec) in doses of 6 and 8 Gy (rats) and 4.5 Gy (guinea pigs). The antiaggregating activity of the vessel wall was determined by the method in [3], by the use of a modified method [8] in the case of guinea pigs; platelet aggregating activity was determined by the formation of malonic dialdehyde (MDA) in the course of thrombin-induced aggregation as in [12], and spontaneous intravascular platelet aggregation was determined by the method in [15]. Healthy animals anesthetized with pentobarbital sodium were used as the donors. The results were subjected to statistical analysis by Student's test and by a variance method.

EXPERIMENTAL RESULTS

The antiaggregating activity of the wall of the abdominal aorta of guinea pigs was found to be only half that of Wistar rats: The corresponding mean values were 39.0 ± 3.5 and 83.0 ± 2.1% ($P < 0.05$). To compare the effect of ionizing radiation on antiaggregating activity of the vessel wall of the two species of animals, the use of the modified method increased the antiaggregating activity of the vessel wall in guinea pigs on average up to 74.0 ± 3.5%. As Table 1 shows, in rats with acute radiation sickness, irradiated in a dose of 6 Gy, antiaggregating activity of the vessel wall was reduced during the first few hours and days, but not statistically significantly. The maximal decrease was observed at the height of the sickness (7th-10th day), and on the 10th day it was reduced by more than half ($P < 0.01$). Antiaggregating activity of the vessel wall began to recover on the 17th day.

After irradiation of rats in a dose of 8 Gy the decrease in antiaggregating activity of the vessel wall was more marked. For instance, antiaggregating activity after 1 and 6 h

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TABLE 1. Antiaggregating Activity of Vessel Wall of Irradiated Animals (in %)

Experimental conditions	Wistar rats		Guinea pigs (4.5 Gy)
	6 Gy	8 Gy	
Control	83,0±2,1%		74,0±3,5
Time after irradiation			
1 h	72±2,7	60±2,9*	39,8±8,3†
6 h	70±5,1	60±4,7*	—
1 day	77±2,7	64±3,1*	63±4,0
3 days	75±1,6	66±2,8	80±2,8
7 days	61±3,5*	46±8,3†	47±2,0†
10 days	31±4,9†	23±0,6†	26±6,5*
17 days	82±0,9	66±3,5	—
30 days	—	64±4,1	69±0,8

Legend. Here and in Table 2: *$P < 0.05$, †$P < 0.01$.

fell on average by 23%, on the 1st and 3rd days by 19 and 17% respectively, on the 7th day by half, and on the 10th day by almost three-quarters ($P < 0.01$); on the 30th day no sign of recovery was observed.

After irradiation of guinea pigs in a dose of 4.5 Gy, antiaggregating activity was reduced by half 1 h after irradiation. The maximal decrease (by almost two-thirds) took place on the 10th day. Recovery was observed after 30 days.

The antiaggregating activity of the vessel wall was thus reduced in acute radiation sickness and the greatest decrease was observed at the height of the disease — during the period of marked hemorrhagic manifestations. Comparison of the dynamic changes in antiaggregating activity of the vessel wall of animals irradiated in lethal (8 Gy) and sublethal (6 Gy) doses reveals the following general rules: 1) the disturbance of antiaggregating activity of the vessel wall under the influence of irradiation is dose-dependent: An increase in the dose of irradiation increases the degree of damage; 2) phase changes in antiaggregating activity of the vessel wall of the irradiated animals corresponded to the periods of development of acute radiation sickness: very slight changes in the initial and early periods, maximal at the height of radiation sickness, followed by normalization during the recovery period.

Since manifestations of the hemorrhagic syndrome of acute radiation sickness in guinea pigs are weaker than in Wistar rats, the data showing the lower antiaggregating activity of the aortic wall in guinea pigs compared with rats makes a definite contribution to our understanding of the mechanism of these differences. For instance, during a marked decrease in

TABLE 2. Platelet Function of Irradiated Wistar Rats

Experimental conditions	MDA formation toward end (5 min) of thrombin-induced platelet aggregation		Index of spontaneous intravascular platelet aggregation (6 Gy)
	6 Gy	8 Gy	
Control	309±39		1,1±0,+
Time after irradiation			
1 h	443±11*	493±24†	3,06±0,28*
6 h	571±38†	605±13†	3,16±0,31*
1 day	543±21*	414±32	3,44±0,55†
3 days	437±56	342±52	3,40±0,38†
7 days	202±25*	217±26	1,83±0,11*
15 days	466±87	—	—
30 days	404±42*	236+46	3,30±0,12*

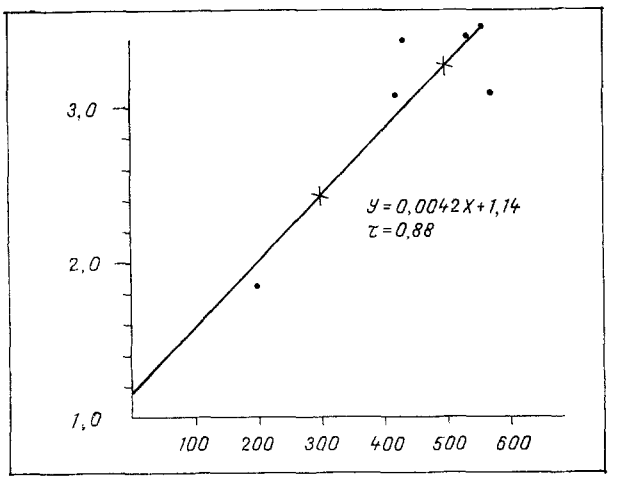

Fig. 1. Changes in MDA concentration and index of intravascular platelet aggregation during the development of acute radiation sickness in rats. Abscissa, MDA concentration (in mM); ordinate, index of spontaneous intravascular platelet aggregation.

synthesis of prostacycline, one of the most powerful endogenous inhibitors of platelet reactions and mainly determining the antiaggregating properties of the vessel wall, and of induction of platelet aggregation by thromboplastic agents formed in the irradiated animal, more favorable conditions are created for intravascular platelet aggregation and for disturbance of microcirculation, and these are components in the pathogenesis of the petechial hemorrhages which arise.

Table 2 gives the results of investigations of platelet function. A significant increase in MDA formation was observed at the earliest stages of development of acute radiation sickness: 1 h after irradiation in a dose of 6 Gy by 43% and in a dose of 8 Gy by 59%; by 85 and 96% respectively 6 h after irradiation. On the 7th day after irradiation MDA formation was reduced on average by 35%, after which it rose again until the 30th day of observation.

The index of spontaneous intravascular platelet aggregation increased on average threefold during the first few hours of development of acute radiation sickness, it remained high on the 1st and 3rd days, and fell at the height of radiation sickness to 1.83 ± 0.11 ($P < 0.05$). By the 30th day no recovery was observed. Changes in platelet function also were phasic in character and depended on the stage of the radiation sickness.

Positive correlation between MDA formation in the platelets and the index of their spontaneous intravascular aggregation is demonstrated in Fig. 1 (coefficient of correlation $r = 0.88$).

The action of γ-rays *in vivo* thus leads to marked changes in the vascular and platelet components of the hemostasis system. The character of the changes shows a definite pattern which corresponds to the stages of development of radiation sickness, and can be observed in two species of laboratory animals which differ in the severity of manifestations of the hemorrhagic syndrome in acute radiation sickness.

The ability of platelets to form MDA in the course of induced platelet aggregation reflects the state of function of the "arachidonic cascade" system [1], whose activation in the platelets leads to synthesis of prostaglandins and thromboxanes (TXA_2 and TXB_2), which are powerful proaggregants and vasoconstrictors [12]. The results suggest the development of an imbalance between arachidonic acid metabolites such as TXA_2 and prostacycline, which leads to the appearance of intravascular platelet aggregation in the early period of development of acute radiation sickness, accompanied by the appearance of aggregation inducers (catecholamines and thromboplastins) in the blood stream, together with reduced antiaggregating activity of the vessel wall.

γ-Ray irradiation in doses causing acute radiation sickness thus initiates not only morphological [6], but also functional injuries to the vascular and platelet components of the hemostasis system, leading to a disturbance of hemostatic hemeostasis.

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