PROSTACYCLINE CONTROL OF PLATELET—VASCULAR WALL HEMOSTASIS DURING IRRADIATION

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An important role in the pathogenesis of the hemorrhagic syndrome in radiation sickness is played by disturbances of equilibrium between platelets and the vascular wall, which are largely due to imbalance between thromoboxane A_2 formation in the platelets and prostacycline (PGI_2) formation in the vascular wall. This leads to the development of intravascular aggregation of platelets and disturbances of their interaction with the blood vessels, factors of great importance for the onset of a syndrome of disseminated blood clotting, leading to various thrombohemorrhagic complications [2]. Inhibition of PGI_2 synthesis in the vascular wall, observed by various workers in radiation sickness [5, 10], is one of the leading factors in this process. Many investigators, analyzing mechanisms of disturbance of prostacycline control of equilibrium in the platelet—vascular wall system, usually assume only that the prostacycline-synthetase activity of the vessels is depressed. However, it has now become clear that realization of the effects of PGI_2 on platelet—vascular wall hemostasis depends not only on the level of PGI_2 formation, but on many other factors also and, in particular, on characteristics of PGI_2 stabilization processes in the blood [6, 7, 11], changes in which during irradiation have virtually not been investigated.

The aim of this investigation was to study the effect of plasma proteins and erythrocytes on the stability of PGI_2 during irradiation.

EXPERIMENTAL METHOD

Experiments were carried out on 180 Wistar rats weighing 150-180 g and on 12 rabbits weighing 2-2.5 kg. Acute radiation sickness was induced by irradiating the animals with ^{60}Co γ-rays in doses of 6 Gy (rats) and 5.45 (rabbits). The antiaggregating activity of the aorta was studied by the method in [8]. Stability of PGI_2 in blood plasma was estimated by determining the degree of preservation of its antiaggregating effect after incubation for 10 min, the ability of erythrocytes to destroy PGI_2 was determined from the degree of diminution of the antiaggregating effect of albumin-stabilized PGI_2 after incubation for 5 min with erythrocytes [6]. Platelet aggregation was measured on an aggregometer of the writers' own design [1]. The numerical results were subjected to statistical analysis by the Student—Fisher test and the Wilcoxon—Mann—Whitney nonparametric test.

EXPERIMENTAL RESULTS

The antiaggregating activity of the vascular wall in irradiated rats showed imprecise changes during the first 3 h after irradiation: In some animals it was increased, in others it was appreciably reduced, but after 1 day it was distinctly reduced. The degree of this reduction was maximal on the 7th-10th day, and on the 14th day there was a tendency toward normalization of this parameter (Fig. 1). These results confirm views according to which PGI_2 formation in the vascular wall is reduced by irradiation, although antiaggregating activity, which many authorities regard as an indicator of PGI_2 production [5], can be accepted in this role only with considerable reservations, for its level can fall on account not only of a decrease in PGI_2 production, but also of an increase in proaggregant formation [3].

Parallel estimation of PGI_2 stabilization showed that the antiaggregating effect of PGI_2 in physiological saline (pH 7.4, 37°C) virtually disappeared after 10 min of incubation (13.6 ± 1.04%); after addition to rat plasma, however, it was 74.7 ± 2.8%, and after addition to rabbit plasma 76.3 ± 2.4%. Compared with the control, plasma of irradiated animals showed

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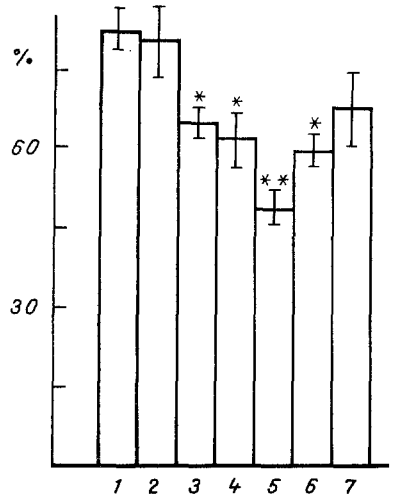

Fig. 1. Antiaggregant effect of rat aorta: 1) control, 2-7) 3 h, and 1, 3, 7, 10, and 14 days respectively after irradiation. Here and in Fig. 2: *P < 0.05, **P < 0.01.

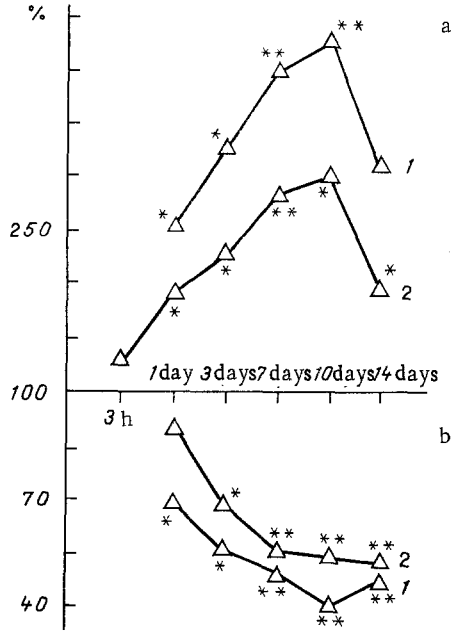

Fig. 2. Changes in stabilizing capacity of plasma proteins (b) and prostacycline-destroying capacity of erythrocytes (a) in irradiated rabbits (1) and rats (2). Abscissa time of observation; ordinate, changes in parameters studied (in % of initial value).

appreciably weaker stabilizing ability. During the first week it fell progressively after only the first day after irradiation in both rats and rabbits (Fig. 2). Conversely, the PGI_2-destroying capacity of erythrocytes of the irradiated animals was increased. Whereas incubation of rabbit erythrocytes in the control reduced the antiaggregating activity of PHI_2 by 13 ± 0.28%, and incubation of rat erythrocytes reduced it by 11.3 ± 0.31% ($P < 0.05$), after irradiation their PGI_2-destroying capacity increased, as early as 1 day, but in particular on the 7th day after irradiation, by 1.5-2.5 times (Fig. 2). We know that erythrocytes and plasma constitute a system which combines many different physiocochemical processes [4].

During irradiation, its state may change considerably due both to change in fractional composition and conformation of the plasma proteins, and to disturbances of the structural and functional organization of the erythrocyte membranes. Since only native serum albumin, and not any other protein fractions, can stabilize PGI_2 [7], changes in the plasma protein spectrum (partial proteolysis, and so on) evidently lie at the basis of changes in the PGI_2-stabilizing ability of the plasma which were discovered. At the same time, disturbances of the functional state of the erythrocyte membranes evidently lead to increased binding of PGI_2, together with its inactivation as a result of transformation into 6-keto-$PG_1\alpha$ [11].

Disturbances of prostacycline control of the functional state of the platelet–vascular wall system during irradiation are thus associated not only with depression of PGI_2 synthesis in the blood vessels, but also, and indeed, but rather, to a decrease in stability of PGI_2 in the blood stream, its more rapid degradation and, as a result of this, the shorter duration and less effective result of its action on platelet–vascular wall hemostasis. This state of affairs must be taken into account when ways of pharmacological correction of the hemorrhagic syndrome are analyzed and, in particular, when it is possible to use infusions of PGI_2 for this purpose, as is increasingly often the case in clinical practice when the therapeutic use of PGI_2 is a possibility [9]. During irradiation, the rapid destruction of PGI_2 in the blood stream may evidently restrict its therapeutic effect considerably, and this calls for appropriate correction of the dosage and methods of administration of PGI_2.

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