HEPARIN-INDUCED HYPERPLASIA OF LYMPHOID TISSUE

B. P. Lukashin

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Experiments on newborn and sexually mature mice and rats showed that repeated injection of heparin leads to an increase both in the number of lymphocytes in the thymus and spleen and in the number of hematopoietic stem cells forming endogenous colonies in the spleen. The lymphoid tissue and the pool of colony-forming units are conjecturally under the regulatory influence of the adrenocortical hormones and of the product of the mast cells – heparin.

KEY WORDS: heparin; bone marrow; spleen; colony-forming units; lymphocytes.

Because of its high content of sulfate groups the heparin molecule has a wide spectrum of biological activity [2, 10, 15]. In particular, this polyanion has an important role in nucleic acid metabolism. Heparin has been shown to stimulate the synthesis of DNA, RNA, and protein in experiments in vivo and in vitro [4, 6, 8, 17]. It might therefore be expected that heparin would stimulate the proliferation of lymphoid tissue and increase the pool of colony-forming units (CFUs) in the bone marrow.

The object of this investigation was to study the effect of heparin on the bone marrow and spleen.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino mice weighing 18-20 g and rats weighing 180-200 g and also on newborn rats. To study the effect of heparin the following parameters were used: the number of leukocytes in the peripheral blood, the number of nucleated cells in the femoral bone marrow and spleen, the number of endogenous colonies in the spleen of mice on the 8th day after irradiation in a dose of 600 R, the body weight, and the weight of the thymus, spleen, and adrenals. Heparin (Richter, Hungary; Spofa, Czechoslovakia) was injected into the animals in a dose of 250 units/kg (and also in a dose of 1000 units/kg for investigation of the peripheral blood) intraperitoneally either all at once or over a period of 8-30 days. The experimental data were subjected to statistical analysis.

EXPERIMENTAL RESULTS

The effects of a single injection of heparin on the peripheral blood of the animals is shown in Fig. 1. In a dose of 250 units/kg heparin produced marked leukocytosis with a maximum in the mice 1 h and in the rats 3 h after injection. With an increase in the dose of heparin the leukocyte count in the peripheral blood also increased. The leukocytosis was caused chiefly by an increase in the number of lymphocytes mobilized from the lymphoid depots [14]. The number of nucleated cells in the bone marrow and spleen of the mice 24 h after a single injection of heparin was the same as in the control.

The results obtained after injection of heparin into sexually mature mice daily for 15 days showed an increase in the number of lymphocytes (Table 1). Despite the twofold increase in the number of nucleated cells in the spleen, the leukocyte count in the peripheral blood and the number of myelokaryocytes in the femoral marrow of the heparinized animals were the same as in the mice of the control group.

Under the influence of heparin marked changes also were found in the experiments on newborn animals. After daily injection of heparin into young rats from the 4th to the 35th day of postnatal life an increase

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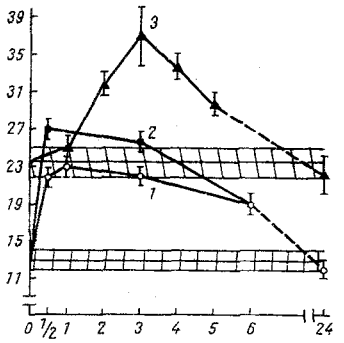

Fig. 1

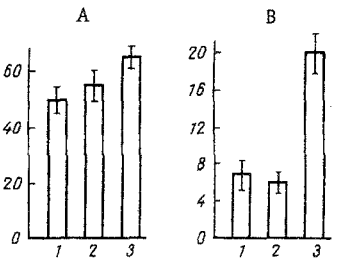

Fig. 2

Fig. 1. Effect of a single injection of heparin on leukocyte count in peripheral blood of mice and rats: 1) mice, 250 units/kg; 2) mice, 1000 units/kg; 3) rats, 250 units/kg. Abscissa, time after injection of heparin (in h); ordinate, leukocyte count (in thousands).

Fig. 2. Effect of heparin injected before or after irradiation on weight of spleen (A) and number of endogenous colonies (B) in mice on the 8th day after irradiation in a dose of 600 R. Abscissa: 1) injection of physiological saline; 2) injection of heparin for 8 days after irradiation; 3) injection of heparin for 15 days before irradiation. Ordinate: A) weight of spleen (in mg), B) number of endogenous colonies.

TABLE 1. Effect of Repeated (for 15 days) Injections of Heparin on the Hematopoietic Organs of Mice

Substance injected	Number of animals	Weight of thymus (in mg)	Weight of spleen (in mg)	Number of nucleated cells (in millions)	
				spleen	bone marrow
Physiological saline	15	51,4±3,3	168±18	165±10	13,5±1,1
Heparin	15	64,0±3,0*	242±26*	352±20*	15,2±1,4

*Here and in Table 2, indices significantly higher than those in the control animals ($P < 0.05$).

TABLE 2. Effect of Repeated (for 30 days) Injections of Heparin into Newborn Rats on Changes in Body Weight and in the Weight of Some Internal Organs

Substance injected	Number of animals	Body weight (in g)	Weight of organs (in mg/100 g body weight)		
			thymus	spleen	adrenals
Physiological saline	25	84,9±4,1	427±18	584±25	33,7±1,1
Heparin	26	91,0±4,5	492±15*	680±21*	39,5±1,2*

was found in the weight of the thymus, spleen, and adrenals (Table 2). The significant increase in weight of the thymus found under these experimental conditions must be particularly emphasized, because this organ plays an important role in lymphopoiesis, metabolism, and immunologic processes [5]. The increase in weight of the adrenals after prolonged administration of heparin takes place chiefly on account of the medulla, whereas the cortex undergoes atrophy [16].

During the investigation of the effect of heparin on the number of endogenous colonies in the spleen the compound was injected daily into the mice of 1 group for 15 days before and in the other group for 8 days after irradiation. Preliminary injection of heparin led to a threefold increase in the number of CFUs

and to a significant increase in weight of the spleen (Fig. 2). Injection of heparin after irradiation had no effect either on the CFU pool or on the weight of the spleen of the irradiated mice.

The results show that the prolonged administration of heparin in a near-therapeutic dose, raising the endogenous blood heparin level by only 50% [10], led to an increase in the number of lymphocytes and in the size of the CFU pool in the bone marrow. By contrast with heparin, adrenocortical hormones reduce the number both of lymphocytes and of CFUs [7, 9].

Under the influence of various adverse factors activation of the pituitary-adrenal system takes place and this, in turn, leads to disintegration of mast cells and to elevation of the endogenous heparin level in the blood [1, 3, 10]. A reaction of this sort, effected by a feedback mechanism by virtue of the antagonism between heparin and glucocorticoids, evidently plays an important role in the maintenance of homeostasis, particularly because, according to some investigators, heparin and heparin-like substances are components of the cytoplasm of all cells [11-13].

There is thus now considerable evidence to show that, besides its anticoagulant function, heparin plays a no less important role in the body as a regulator of enzymic and hormonal activity [1, 2, 3, 10, 15]. This evidently lies at the basis of the observed effect of heparin on the hematopoietic tissues.

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