EFFECT OF HEPARIN ON VASCULAR PERMEABILITY DISTURBED BY HISTAMINE

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Experiments on albino rats have shown that heparin, when injected intramuscularly in a dose of 2 i.u./100 g, reduces vascular permeability previously increased by exogenous and endogenous histamine.

Exogenous histamine was injected intravenously as a 0.02% solution. Liberation of endogenous histamine was obtained by intraperitoneal injection of 5% dextran solution.

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Clinical investigations have shown that heparin has an antiexudative action [2, 8]. However, some experimental findings do not confirm this conclusion [1, 10].

Since histamine plays an important role in the mechanism of disturbance of vascular permeability in many pathological processes, it seemed worthwhile studying the effect of heparin on vascular permeability when disturbed by endogenous and exogenous histamine.

EXPERIMENTAL METHOD

Experiments were carried out on sexually mature albino rats weighing 150-200 g. The state of the vascular permeability was determined from escape of the dye, Evans blue, from the blood. The dye was injected intravenously in the form of a 0.5% solution in a dose of 0.25 μg/100 g. The concentration of dye in the blood was measured in the FÉK-M1 photoelectric colorimeter 1 h after injection.

Histamine was injected intravenously as a 0.02% solution in a dose of 200 μg/100 g body weight 30 min after injection of the dye. To liberate endogenous histamine, the rats were injected intraperitoneally (30 min after injection of the dye) with 5% dextran solution (100 mg/100 g).

According to the findings of E. I. Krichevskaya and E. V. Kapitonova [4], 1 h after injection of dextran into rats in a dose of 500 mg/kg a considerable decrease in the histamine content is observed in its principal depots: the skin, stomach, and liver. Heparin was injected intramuscularly in a dose of 5 i.u./100 g. The first injection was given 2 min before injection of the dye and the second 30 min later.

The fibrinolytic activity of the blood was determined by the method of M. A. Kotovshchikova and B. I. Kuznik [3]. Since the fibrinolytic activity of rats' blood is very high, the period of incubation of the blood was shortened to 1 h.

EXPERIMENTAL RESULTS

Injection of heparin into 15 rats caused the fibrinolytic activity of the blood to increase after 30 min from 25.6±1.8 to 37.7±3.5% ($P < 0.01$). In the experiments of series I the effect of heparin on vascular permeability previously increased by exogenous histamine was studied. The results are given in Table 1, which shows that injection of histamine was accompanied by a considerable increase of vascular permeability, as shown by the lower concentration of dye in the blood of these rats compared with the controls. If heparin was injected twice in doses of 5 i.u./100 g (the first injection 2 min before injection of histamine and the second immediately thereafter), no appreciable disturbances of vascular permeability were observed in the experimental animals.

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TABLE 1. Effect of Histamine and Heparin on Concentration of Dye in the Blood

Experimental conditions	No. of rats	Concentration of dye in blood (in μg/ml)	P
Control	10	45.80±0.58	
Histamine	10	31.77±2.01	P < 0.001
Histamine + heparin	10	45.57±2.27	P' < 0.01
Heparin	7	47.57±3.59	

Note. P' relative to rats receiving histamine

TABLE 2. Effect of Dextran and Heparin on Concentration of Dye in the Blood

Experimental conditions	No. of rats	Concentration of dye in blood (in μg/ml)	P
Control (I)	10	45.80±0.58	
Dextran (II)	15	25.22±2.24	P < 0.001 I-II
Dextran + heparin (II)	15	37.22±2.22	P < 0.001 II-III

When injected into control rats, heparin had no significant effect on vascular permeability. Other authors have reached similar conclusions [5].

In the experiments of series II the effect of heparin on vascular permeability previously disturbed by endogenous histamine was studied. The results of these experiments are given in Table 2.

As Table 2 shows, injection of dextran caused a sharp increase in vascular permeability. This may be explained by liberation of a large quantity of endogenous histamine. According to reports in the literature, 15 min after intravenous injection of dextran the blood histamine concentration is increased by 50 times [9]. Heparin caused a significant decrease in vascular permeability previously disturbed by the endogenous histamine liberated in response to injection of dextran.

Hence, heparin influenced the vascular permeability when disturbed by both exogenous and endogenous histamine. This effect may be regarded as a result of the direct inactivation of histamine by heparin. According to reports in the literature heparin can fix histamine in vitro [12], 1 mg heparin binding 200 μg of histamine.

The effect of heparin on the fibrinolytic activity of the blood is also of definite importance in the mechanism of its action on vascular permeability. Small doses of heparin activate fibrinolysin [11]. This was observed in our experiments also. Injection of activated fibrinolysin into animals, according to the observations of some workers [6, 7], reduces the degree of disturbance of capillary permeability produced by histamine.

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