MECHANISM OF THE PHLOGOGENIC ACTIVITY OF LEUKOCYTES

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Experiments on rabbits and rats to which substances with antihistamine, antibradykinin, and antiproteolytic activites were administered showed that the phlogogenic activity of the leukocytes is linked with the action of proteolytic enzymes and kinins and, to a lesser degree, with histamine.

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Recent investigations have extended our knowledge of the role of leukocytes in the principal manifestations of inflammation [7, 10, 11, 15, 16]. An important place in the mechanism of this leukocyte activity has been ascribed to histamine [11, 12]. Later work has demonstrated that leukocytes contain cathepsins – kinin-forming and kinin-destroying enzymes [17]. However, the role of these leukocytic enzymes in inflammation has not been investigated.

The object of this investigation was to continue the study of the mechanisms of the phlogogenic activity of leukocyte factors.

EXPERIMENTAL METHOD

Experiments were carried out on 60 chinchilla rabbits (2.5-3.5 kg) and 70 Wistar rats (200-250 g) of both sexes. The leukocyte preparations were obtained by the method described previously [5] and injected intradermally into the experimental animals in 0.1 ml physiological saline. The dose of injected material was calculated per mg protein, determined by Lowry's method [14]. The dose of fragmented leukocytes injected varied from $67 \cdot 10^3$ to $870 \cdot 10^3$/0.1 ml. The development of disturbances of permeability of the skin vessels 30 min after the injection served as index of the phlogogenic action of the lysosomes, granulocytic material, and destroyed leukocytes. Permeability of the skin capillaries was studied by the standard method [6]. The dye Evans' blue was injected in 1% solution in a dose of 20 mg/kg body weight. The phlogogenic activity of the leukocyte preparations in the experimental animals was determined after administration of various pharmacological agents. The antihistamine agent used was dimebolic (10 mg/kg intraperitoneally). Dimedrol (benadryl), combining antihistamine with antibradykinin properties [2], was injected in the same doses as dimebolin. Trasylol was injected intraperitoneally in a dose of 2000 kallikrein units/kg as inhibitor of proteolysis. The phlogogenic activity of the leukocyte preparations was determined in control animals (20 rabbits and 20 rats) not receiving these pharmacological agents.

The results were subjected to statistical analysis by Fisher's method for fourfield tables [4].

EXPERIMENTAL RESULTS

Dimedrol proved to be the most effective antiinflammatory preparation, considerably inhibiting the development of disturbances of vascular permeability in the skin of rabbits and rats after injection of lysosomes, granulocytic material, and fragmented leukocytes (Table 1). If the dose of leukocytic preparations was increased, the efficacy of dimedrol remained high in the experiments on rabbits but was reduced in rats. Trasylol and dimebolin also inhibited the action of leukocytic preparations on vascular permeability in the skin, although to a lesser degree than dimedrol. For instance, with the doses of leukocytic preparations used (0.01-0.05 mg protein), an antiinflammatory effect of trasylol was observed in rabbits after injection of all three preparations, but in rats it was well marked only after injections of granulocytic material

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TABLE 1. Effect of Dimedrol, Dimebolin, and Trasylol on Inflammatory Activity of Homologous Leukocyte Preparations

Dose of protein injected (in mg)	Dimedrol			Dimebolin			Trasylol		
	I	II	III	I	II	III	I	II	III
				Rats					
0,01	0/10*	1/12*	0/6*	1/10*	5/10	3/6	4/9	0/6*	6/14*
0,05	1/8*	5/17*	0/6*	6/12*	12/22*	4/6	4/6	1/6*	4/12*
				Rabbits					
0,01	1/13*	0/13*	0/6*	2/11*	1/6*	1/6*	1/8*	0/6*	1/6*
0,05	0/6*	0/8*	0/6*	0/6*	8/11	6/6	1/6*	1/6*	1/6*

* $P < 0.01$ compared with control (in control experiments injection of all stated doses of leukocytic preparations caused the development of permeability disturbances in all 20 cases).
Note: I) fragmented leukocytes; II) granulocytic material; III) lysosomes. Numerator) number of cases with disturbance of permeability; denominator) total number of cases.

and lysosomes. Dimebolin had an antiinflammatory action in rabbits after administration of all the leukocytic preparations in the doses indicated above, but in rats it was effective chiefly after injection of fragmented leukocytes.

The antiinflammatory action of substances with antihistamine, and with antihistamine and antibradykinin properties, and also of the proteolytic inhibitor indicates the complexity of the mechanism of phlogogenic activity of the leukocytes. The work of Janoff and co-workers [11, 12] has shown that histamine participates in the development of the inflammatory reaction on the mesentery in rats produced by leukocytic lysosomes. In the present experiments, dimedrol, with an antihistamine activity 95 times weaker than that of dimebolin [1, 3], had a stronger action than dimebolin, indicating the negligible role of histamine in the development of the inflammatory reaction following intradermal injection of leukocytic preparations. The inhibitory action of dimedrol in these experiments may have been due to its antibradykinin activity. Evidence of this is also given by the antiinflammatory action of trasylol, an inhibitor of proteolysis and kinin formation [9]. The results of these experiments indicate that an important role in the development of disturbances of vascular permeability in the skin following injection of lysosomes and granulocytic material is played by the proteolytic enzymes of the leukocytes, in agreement with other findings [7, 8, 13].

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