

EFFECT OF HISTAMINE AND THYMALINE ON BLOOD COAGULABILITY
AND FIBRINOLYSIS IN INTACT AND THYMECTOMIZED RATS

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The writers showed previously that blood clotting is accelerated and fibrinolysis inhibited in thymectomized rats 2-4 months after the operation [8, 11, 15]. After thymectomy responses of the hemostasis system to adrenalin also are considerably modified. Preliminary injection of the thymus preparation thymaline, a modulator of cellular immunity [14], for 1 week restores the adequacy of responses of blood clotting and fibrinolysis to adrenalin [8]. Histamine sharply increases the rate of blood clotting and stimulates fibrinolysis [4, 5, 9].

The object of this investigation was to study the reaction of the hemostasis system to histamine in thymectomized animals and to determine the effect of preliminary administration of thymaline on this process.

EXPERIMENTAL METHOD

Altogether 93 male rats were used. The thymus was removed from 61 of the animals at the age of 1.5-2 months, and the other 32 rats remained intact. The experiments were carried out 2-3 months after the operation. Histamine was injected in a dose of 0.00012 mg/kg body weight into all animals and 26 of the thymectomized rats received an injection of thymaline in 0.5% procaine solution (1 mg per rat) in the course of 1 week. The blood clotting plasma recalcification, cephalin, kaolin, prothrombin, and thrombin times, activity of factors V and VII, total antithrombin activity, fibrinogen concentration, euglobulin lysis time, and Hageman-dependent fibrinolysis of control and thymectomized animals were determined and the ethanol test carried out [2].

These parameters were studied 10 min after injection of histamine. Intact and thymectomized rats (receiving or not receiving thymaline), into which the corresponding volume of physiological saline was injected instead of histamine, served as the control.

EXPERIMENTAL RESULTS

The rats developed marked hypercoagulation 2-3 months after thymectomy: The blood clotting and plasma recalcification times and the kaolin and cephalin times were shortened, the concentrations of factors V and VII were increased, the prothrombin and thrombin time were reduced, and the fibrinogen concentration increased. The development of hypercoagulation after thymectomy in the rats can be attributed primarily to shortening of the first phase of blood clotting — prothrombinase formation. Evidence in support of this view is given by the increase in concentrations of factors V and VII and the decrease in the prothrombin, kaolin, and cephalin times. Moreover, in the thymectomized rats total and Hageman-dependent euglobulin fibrinolysis was inhibited, possibly on account of a decrease in the activating and an increase in the inhibitory component of fibrinolytic activity of the blood. Injection of thymaline for 1 week into the thymectomized animals as a rule restored these parameters of blood clotting and fibrinolysis to the characteristic values for intact rats.

In the intact rats histamine accelerated blood clotting, reduced the recalcification,

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TABLE 1. Effect of Histamine on Blood Coagulability and Fibrinolysis in Intact and Thymectomized Rats Receiving and Not Receiving Thymus Factor (Thymaline) (M \pm m)

Parameter studied	Rats undergoing mock operation (control)		Thymectomized rats not receiving thymaline (experiment 1)		Thymectomized rats receiving thymaline (experiment 2)	
	before injection of histamine	after injection of histamine	before injection of histamine	after injection of histamine	before injection of histamine	after injection of histamine
Blood clotting time, sec	235,76 \pm 13,59	165,9 \pm 4,49*	181,22 \pm 6,04 †	150,09 \pm 7,51*	213,29 \pm 12,13 ‡	169,29 \pm 5,08*
Plasma recalcification time, sec	70,2 \pm 4,83	54,6 \pm 3,0*	64,37 \pm 2,85	57,75 \pm 0,99*	66,2 \pm 2,78	57,4 \pm 1,55*
Prothrombin time, sec	19,4 \pm 1,17	16,7 \pm 1,8	16,91 \pm 0,62	15,23 \pm 0,9	18,18 \pm 2,67	16,64 \pm 1,43
Cephalin time, sec	63,57 \pm 2,79	53,74 \pm 4,05	57,28 \pm 2,23	36,14 \pm 3,07*	67,28 \pm 2,09 ‡	57,0 \pm 2,51*
Kaolin time, sec	42,85 \pm 1,67	36,57 \pm 2,79*	39,0 \pm 1,25	28,0 \pm 1,25*	48,28 \pm 1,96 ‡	42,71 \pm 1,12*
Factor V, sec	24,44 \pm 2,58	30,44 \pm 2,02	21,56 \pm 1,69	27,0 \pm 2,25	23,33 \pm 2,47	28,89 \pm 1,69
Factor VII, sec	57,28 \pm 4,47	72,14 \pm 4,19*	48,44 \pm 2,47	55,0 \pm 2,58	55,0 \pm 2,25	62,44 \pm 2,36*
Thrombin time, sec	31,52 \pm 0,95	26,71 \pm 0,86*	27,38 \pm 1,01 †	24,88 \pm 0,62*	32,66 \pm 1,06 ‡	28,88 \pm 0,99*
Total antithrombin activity, sec	8,66 \pm 1,14	8,42 \pm 1,77	6,8 \pm 0,61	6,5 \pm 2,24	10,5 \pm 0,71 ‡	6,0 \pm 1,25*
Ethanol test	+	++	++	+++	++	++
Fibrinogen, mg	14,7 \pm 0,77	16,7 \pm 0,7	16,85 \pm 0,63 †	18,5 \pm 0,55	16,6 \pm 1,48	16,2 \pm 1,0
Hageman-dependent fibrinolysis, min	24,71 \pm 2,37	15,86 \pm 2,51*	31,14 \pm 6,7	19 \pm 4,75	19,71 \pm 2,23	11,85 \pm 1,82*
Total euglobulin fibrinolysis, min	198,2 \pm 9,88	158,7 \pm 8,98*	275 \pm 28,61 †	204,47 \pm 17,05*	195,68 \pm 18,44 ‡	150,0 \pm 9,57*

Legend. *P < 0.05 for comparison before and after injection of histamine; †the same, between control and experiment 1, before injection of histamine; ‡the same, between experiment 1 and experiment 2, before injection of histamine.

kaolin, cephalin, and prothrombin times, and very slightly lowered the concentrations of factors V and VII, increased the fibrinogen concentration, and activated fibrinolysis (Table 1). After injection of histamine, Hageman-dependent fibrinolysis also was stimulated, and this may be evidence that activation of kallikrein took place through the intervention of Hageman factor [3].

There is no doubt that the acceleration of blood clotting and stimulation of fibrinolysis after injection of histamine were largely connected with the release of thromboplastin and plasminogen activator from the vascular wall and endothelium of the heart [1, 5, 9, 13]. Histamine is also known to bind heparin, and this can shorten the prothrombin time [12].

Injection of histamine into thymectomized rats is accompanied by marked shortening of the blood clotting, plasma recalcification, cephalin, kaolin, and thrombin times and by elevation of the fibrinogen level. However, if this response is compared with that observed in intact rats after injection of histamine, a clear difference will be seen between them. In thymectomized rats marked hypercoagulation was already observed before injection of thymaline. Injection of histamine increased blood coagulability even more. Under these circumstances the blood clotting, kaolin, and cephalin times were considerably shorter than in intact animals receiving histamine.

Apparently marked stimulation of total and Hageman-dependent fibrinolysis takes place in thymectomized rats under the influence of histamine. Yet fibrinolysis in these animals is sharply inhibited. After injection of histamine, although fibrinolysis is considerably stimulated, it does not reach the values characteristic of intact animals.

It can thus be concluded that an imbalance develops between the acceleration of blood clotting and stimulation of fibrinolysis in the thymectomized rats. This evidently largely accounts for the mortality among the thymectomized animals after injection of histamine. For instance, four of the 26 intact animals and 15 of the 31 thymectomized rats died (P < 0.05). Massive intravascular clots were found in all thymectomized rats after autopsy in the chambers of the heart and in the great vessels. Often it was impossible to draw blood up into the syringe from such animals because it clotted in the needle.

Thymaline not only restored an adequate response of blood clotting and fibrinolysis in the thymectomized rats to histamine, but it also prevented death of the animals (none of the 26 rats died in this series).

Consequently, injection of histamine stimulates latent polymicrocoagulation, as shown by the data obtained by the writers previously [5] and also by the enhancement of the ethanol test found in the present experiments. A particularly sharp increase in the intensity of blood clotting was observed in thymectomized animals after injection of histamine. It can be tentatively suggested that insufficient stimulation of fibrinolysis in thymectomized animals does not lead to lysis of clots which have formed, and this is one of the causes of death of the rats after withdrawal of blood. Similar results were obtained after injection of thrombin [6]. The data are evidence that the systems of immunogenesis and hemostasis are intimately interlinked with one another and possess regulatory mechanisms [6, 8, 10, 11, 15].

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