EFFECT OF ADRENALIN AND THYMUS FACTOR ON BLOOD CLOTTING AND FIBRINOLYSIS IN HEALTHY AND THYMECTOMIZED RATS

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The writers showed previously [8] that 2-4 months after thymectomy in rats, hypercoagulation develops and fibrinolysis is inhibited.

These observations show that there is a close link between cellular immunity, controlled by the thymus, and hemostasis. The object of the present investigation was to study how blood clotting and fibrinolysis are regulated after removal of the thymus. Adrenalin was chosen as a drug which has a marked effect on blood clotting and fibrinolysis [1, 2, 4, 6, 7, 10, 12].

EXPERIMENTAL METHOD

Experiments were carried out on 90 rats of both sexes. The thymus was removed from 60 of them at the age of 2 months. All experiments were conducted 2-4 months after the operation. There were three series of investigations: In series I adrenalin was injected (0.00025 mg/kg body weight) into 30 rats after a mock operation, and 10 min later changes in blood clotting and fibrinolysis were studied. In series II the same procedures were carried out on 30 thymectomized rats. In series III thymus polypeptide factor [11] was injected intramuscularly into 30 thymectomized rats in a dose of 1 mg daily for 7 days, after which the experiments with adrenalin were carried out.

The blood clotting time, plasma recalcification time, prothrombin and thrombin times, activity of factors V and VII, the fibrinogen concentration, ethanol test, euglobulin lysis time, and activity of fibrinolytic agents obtained from the euglobulin fraction [3] were investigated. Simultaneously with the experiments, a control test was always carried out on rats undergoing the mock operation and thymectomized rats, receiving or not receiving the thymus polypeptide factor, but which were given the same volume of physiological saline instead of adrenalin solution.

The results were subjected to statistical analysis and the level of significance was calculated.

EXPERIMENTAL RESULTS

The rats developed hypercoagulation 2-4 months after thymectomy: The blood clotting time was considerably shortened, the fibrinogen concentration rose a little, and a tendency was noted for the recalcification time and prothrombin time to be reduced and for fibrinolysis to be inhibited ($P < 0.2$). In animals receiving thymus factor for 1 week, none of the indices studied differed significantly from normal (Table 1).

After administration of adrenalin to the rats undergoing the mock operation the blood clotting time, recalcification time, and fibrinogen concentrations were reduced and fibrinolysis was stimulated significantly. The results agree on the whole with data in the literature [4, 6, 8, 12].

In thymectomized rats adrenalin also led to the development of hypercoagulation and stimulation of fibrinolysis. Meanwhile the results of the experiments on thymectomized animals

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TABLE 1. Effect of Adrenalin on Blood Clotting and Fibrinolysis in Rats Undergoing Mock Operation and in Thymectomized Rats Receiving and Not Receiving Thymus Factor (M ± m)

Index studied	Rats undergoing mock operation (control)		Thymectomized rats (experiment I)		Thymectomized rats (experiment II)	
	A	B	A	B	A	B
Blood clotting time, sec	236,8±13,8	187,6±8,4*	176,0±6,2†	159,0±6,6	224,9±8,8‡	195,4±7,7*
Plasma recalcification time, sec	75,1±4,6	62,5±3,8*	68.2±3,7	72,3±4,4	71,6±3,3	72,3±4,8
Prothrombin time, sec	17,6±1,03	16,9±0,92	15,6±0,4†	14,8±0,3	17,3±0,57‡	15,5±0,57
Factor V, sec	29,8±1,8	32,7±2,1	27,9±1,8	28,7±1,6	31,1±2,2	30,6±2,4
Factor VII, sec	43,1±3,1	44,7±2,2	40,8±2,04	41,5±2,4	43,8±2,6	43,1±1,9
Thrombin time, sec	28,0±5,08	26,5±1,7	23,9±1,1	25,3±1,6	27,6±1,1	23,2±1,3*
Fibrinogen, mg	14,9±0,9	13,5±0,8	17,0±1,4	14,2±1,04*	15,4±0,9	15,2±1,1
Ethanol test						
Lysis of euglobulins, min	205,3±25,4	134,3±10,5*	266,3±38,5	187,5±20,8*	201,1±21,0	139,5±11,2*
Plasmin (zone of lysis, mm^2)	34,5±5,0	28,5±5,8	15,7±2,0†	21,5±4,0	27,5±4,0‡	30,2±6,0

*P < 0.05; significance of difference between A and B.
†P < 0.05 between control (A) and experiment I (A).
‡P < 0.05 between experiment I (A) and experiment II (A).
Legend. A) Before injection of adrenalin; B) after injection of adrenalin; experiment I) rats not receiving thymus factor; experiment II) receiving thymus factor.

differed from those obtained on rats undergoing the mock operation. In the thymectomized rats, adrenalin led to a smaller decrease in clotting time, a strongly positive ethanol test was more frequently observed, and the fibrinogen concentration was reduced.

Just as in animals undergoing the mock operation, fibrinolysis was stimulated in the thymectomized rats after injection of adrenalin. However, its activation did not reach the same level as in the healthy rats. The data suggest that after thymectomy the reserve capacity of fibrinolysis is exhausted and it cannot be adequately stimulated in response to injection of adrenalin.

Preliminary injection of thymus factor into thymectomized rats largely restores the response of the various indices of the blood clotting system and fibrinolysis to injection of adrenalin.

Acceleration of blood clotting in the thymectomized rats was due primarily to the more rapid formation of prothrombinase, as shown by reduction of the prothrombin time. The possibility cannot be ruled out that the development of hypercoagulation was to some extent due to a disturbance of immunologic control over the concentrations of blood clotting factors in thymectomized animals.

Observations showed that inhibition of fibrinolysis in thymectomized rats was associated with a fall in the plasmin level ($P < 0.05$).

The results are evidence not only of a link between immunogenesis, on the one hand, and hemostasis and fibrinolysis, on the other hand, but also that the mechanisms of regulation of these processes are common.

This last conclusion is confirmed by experiments in which the effect of adrenalin on blood clotting and fibrinolysis was studied in rats undergoing the mock operation and in thymectomized rats. Adrenalin accelerates blood clotting and stimulates fibrinolysis, possibly due to the liberation of thromboplastin and plasminogen activator from intact arteries and veins [6, 10, 12], and also to stimulation of Hageman factor [2]. Blood clotting in thymectomized rats was stimulated to a lesser degree by adrenalin. This can be explained on the grounds that marked hypercoagulation was present already in these rats in the resting state. There is, as we know, a limit to the acceleration of blood clotting, and when this is reached, secondary hypocoagulation develops [5, 9]. This may possibly be the explanation of the fact that in thymectomized rats the recalcification time was practically unchanged after injection of adrenalin.

In thymectomized animals fibrinolysis is activated less strongly after injection of adrenalin, and it does not reach the characteristic level found in rats after the mock operation, when intravascular blood clotting can be induced on a considerable scale.

Injection of thymus polypeptide factor daily for 7 days into the animals not only restored normal blood clotting and fibrinolysis, but also restored the adequate response of the hemostasis system to injection of adrenalin. Thymus factor is known to promote differentiation of T lymphocytes. At the same time, it intensifies fibrinolytic activity. However, no direct connection has been established between these two effects. It can only be postulated that such a link exists, for in old age hypercoagulation develops and fibrinolysis is inhibited [1, 5, 9]. By this age partial involution of the thymus has taken place. It is possible that these processes are interlinked very closely. If this suggestion is true, it can be hoped that the use of thymus polypeptide factor in old age will help not only to normalize cellular immunity [11], but also to prevent the development of thrombosis and embolism.

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