EFFECT OF THYMALIN ON THE STATE OF THE BLOOD KALLIKREIN-KININ SYSTEM IN THYMECTOMIZED RATS

V. I. Kiselev, B. I. Kuznik,
V. N. Kurasov, V. A. Treshchutin,
V. G. Morozov, V. Kh. Khavinson,
and D. R. Khyshova

UDC 616.438-089.87-07:[616.153.1:577.152.34[616.154:577.175.85]-02:615.362.438

KEY WORDS: kallikrein-kinin system; kallikrein; kininogen; thymalin.

Thymectomy in various animals causes the development of hypercoagulation and inhibition of fibrinolysis in them 3 months after the operation. Injection of a low-molecular-weight factor from the thymus, namely thymarin (medicinal form – thymalin) into thymectomized animals not only restores normal coagulability of the blood and fibrinolysis, but also restores adequate reactions of the hemostasis system to various neurohumoral stimuli [5-7]. The blood clotting and fibrinolysis system is known to be functionally connected with the kallikrein-kinin system [2, 3, 14-16].

The aim of this investigation was to determine the role of the thymus in regulation of the state of the kallikrein-kinin system.

EXPERIMENTAL METHOD

Experiments were carried out on 38 albino rats from which the thymus gland was removed at the age of 1.5-2 months. The animals were killed 3 months after the operation. Blood for investigation of the components of the plasma kallikrein-kinin system was taken from the superior vena cava by a siliconized syringe into a siliconized vessel. After centrifugation at 3000 rpm for 30 min the blood plasma was separated and the following components were determined in it: kininogen [8, 13], total kallikrein activity [9], and activity of kinin-destroying plasma enzymes [14]. Animals undergoing mock operations, kept under conditions identical with those of the experimental group, served as the control.

EXPERIMENTAL RESULTS

Considerable changes in the state of the plasma kallikrein-kinin system were found in the thymectomized animals (Table 1).

These changes were manifested in the experimental group by a 1.8-fold increase in kallikrein activity. A marked fall in the kininogen level (by 2.7 times) was observed. A decrease in the content of the substrate (kininogen) for the formation of active kinins is a characteristic sign of activation of kinin formation. Meanwhile activity of the kinin-destroying plasma enzymes in the experimental animals did not differ from that in the control ($P > 0.5$).

The results are evidence that thymectomy leads to a significant increase in the intensity of kinin formation, accompanied by hyperproduction of active kinin. In the next series of experiments thymalin was injected intramuscularly into thymectomized rats in a dose of 0.07 mg per injection in 0.2 ml of physiological saline daily for 7 days. It will be clear from Table 1 that injection of thymalin completely prevented the increase in kallikrein activity observed in the thymectomized animals. Its activity was lowered by 2.9 times compared with rats of the experimental group, which did not receive thymalin after thymectomy.

Department of Normal Physiology, Altai Medical Institute. Department of Normal Physiology, Chita Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR N. V. Vasil'ev.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 99, No. 6, pp. 654-656, June, 1985. Original article submitted November 16, 1984.

 0007-4888/85/9906-0696$09.50

TABLE 1. State of the Plasma Kallikrein-Kinin System in Rats Undergoing Mock Operations (A) and Thymectomized Rats (B) and Thymectomized Rats Receiving Thymalin (C)

Parameter studied	n	A	n	B	n	C	P
Kallikrein activity, μg/ml plasma	10	0,56±0,07	8	1,01±0,15	10	0,35±0,15	$P_1<0,05$ $P_2<0,01$ $P_3<0,2$
Kininogen concentration, μg/ml plasma	9	6,10±1,61	8	2,26±0,66	10	7,64±0,77	$P_1<0,05$ $P_2<0,001$ $P_3<0,2$
Kininase activity, μg/plasma·min	8	2,61±0,24	8	2,92±0,16	7	2,18±0,34	$P_1>0,5$ $P_2>0,1$ $P_3>0,2$

Legend. P_1) Significance of difference between parameters for experimental (thymectomized) and control (mock operation) groups of animals; P_2) between experimental groups (thymectomy + thymalin compared with thymectomy alone); P_3) between experimental group (thymectomy + thymalin) and animals undergoing mock operation (control).

Thymalin not only abolished the increase in activity of the enzyme in the thymectomized rats, but actually reduced it below the control level. This showed that in the presence of an excess of thymalin, activity of the trigger enzyme of the kinin cascade (kallikrein) is reduced.

The plasma kininogen level in the thymectomized rats receiving thymalin was considerably (by 3.4 times) higher than in animals not receiving thymalin, but did not differ from its level in rats undergoing the mock operation. Administration of thymalin for 7 days thus completely prevented the activation of kinin formation observed in the animals 3 months after thymectomy. Inhibition of kallikrein activity was evidently due to injection of an excess of thymalin, and could serve as additional proof of the participation of the thymus in the humoral regulation of activity of the blood plasma kallikrein-kinin system.

The writers showed previously that hypercoagulation develops and fibrinolysis is inhibited in thymectomized rats [4, 10, 11]. These changes are abolished by thymalin [5-7]. There is no doubt about the fact that acceleration of blood clotting after thymectomy in rats may be explained to some degree by elevation of the levels of kallikrein and kinins which participate in activation of the contact phase of blood coagulation.

The results are evidence that the thymus influences not only blood coagulation and fibrinolysis, but also the processes of kinin production.

LITERATURE CITED

1. P. Ya. Gaponyuk and E. M. Umarkhodzhaev, Patol. Fiziol., No. 5, 80 (1969).
2. O. A. Gomazkov and N. V. Komissarova, Usp. Sovrem. Biol., 82, No. 3, 356 (1976).
3. V. I. Kiselev, A. M. Ryzhkov, V. P. Kulikov, et al., Ter. Arkh., No. 12, 87 (1982).
4. B. I. Kuznik, N. N. Tsybikov, V. Medvedev, et al., in: Physiology and Pathology of the Hemostasis System [in Russian], Chita (1980), p. 30.
5. B. I. Kuznik, V. G. Morozov, L. I. Pisarevskaya, et al., Byull. Éksp. Biol. Med., No. 9, 264 (1981).
6. B. I. Kuznik, L. I. Pisarevskaya, V. G. Morozov, et al., Byull. Éksp. Biol. Med., No. 9, 27 (1982).
7. B. I. Kuznik, N. N. Tsybikov, L. I. Pisarevskaya, rt al., Byull. Éksp. Biol. Med., 95, No. 2, 26 (1983).
8. T. S. Paskhina, G. P. Egorova, A. L. Laufer, et al., in: Modern Methods in Biochemistry [in Russian], Part 2, Moscow (1968), p. 205.
9. M. S. Surovkina, Lab. Delo, No. 1, 6 (1975).
10. D. R. Khyshova, L. I. Pisarevskaya, G. Ch. Makhakova, et al., Byull. Éksp. Biol. Med., No. 10, 26 (1983).
11. N. N. Tsybikov, Patol. Fiziol., No. 6, 65 (1980).
12. N. N. Tsybikov, B. I. Kuznik, N. L. Molchanova, et al., Probl. Éndokrinol., No. 4, 77 (1982).
13. C. R. Diniz and I. F. Carvalho, Ann. N. Y. Acad. Sci., 104, 77 (1963).
14. A. P. Kaplan, Life Sci., 16, 803 (1975).
15. A. P. Kaplan, J. Invest. Derm., 67, No. 5, 635 (1976).
16. A. P. Kaplan, Semin. Thromb. Hemost., 3, 1 (1976).