MECHANISM OF HYPOPROTHROMBINEMIA AND HYPOPROCONVERTINEMIA IN EXPERIMENTAL THYROTOXICOSIS

N. N. Petrishchev and V. I. Kiyanov

UDC 616.441-008.61-092.9-07:616.151.514-07

Indices of the thromboelastogram (TEG) and the activity and breakdown of prothrombin and proconvertin in experimental thyrotoxicosis were studied in experiments on rats. In the presence of marked thyrotoxicosis most of the indices of the TEG shifted toward hypocoagulation: thrombin formation was slowed, the total coagulation constant was increased, and maximal amplitude was reduced. A decrease in the activity and intensified breakdown of prothrombin and, in particular, of proconvertin also were observed. It is postulated that increased destruction of these factors plays a fundamental role in the pathogenesis of the hypoprothrombinemia and hypoproconvertinemia accompanying thyrotoxicosis.

KEY WORDS: prothrombin; proconvertin; thyrotoxicosis.

In patients with thyrotoxicosis, especially a severe form, the prothrombin and proconvertin levels are lowered [1, 3, 5, 7, 10-13]. Some workers consider that this is because of liver damage [2, 5, 8, 10]. There is evidence of increased destruction of procoagulants in hypothyroidism [14].

The object of this investigation was to study the metabolism of prothrombin and proconvertin in experimental thyrotoxicosis.

EXPERIMENTAL METHOD

Thyrotoxicosis was induced by administration of thyroid extract (300 mg/100 g body weight) to sexually mature albino rats for 7-8 days. Animals whose weight was reduced by 20-25% were used in the experiments. Blood clotting was studied by the thromboelastographic method (with the "Tromb-1" apparatus). Prothrombin activity was determined by Quick's method in V. N. Tugolukov's modification, and proconvertin activity by Owren's method in the modification of K. G. Kapetanaki and M. A. Kotovshchikova. To determine the intensity of prothrombin and proconvertin breakdown, the method of pharmacokinetic analysis based on blocking the synthesis of these factors was used [16]. The breakdown constant (K_b) of the factor and the biological half-life ($T_{1/2}$) are related as follows: $T_{1/2} = 0.693/K_b$. The level of synthesis (L_S) was determined as $L_S = K_b \cdot A$, where A is the activity of the factor [17]. The synthesis of prothrombin and proconvertin was blocked by oral administration of phenindione in a dose of 5 mg/100 g body weight [4].

EXPERIMENTAL RESULTS AND DISCUSSION

In marked thyrotoxicosis most of the indices of the thromboelastogram were shifted toward hypocoagulation. Thrombin formation was slowed, the total, nonspecific, and specific coagulation constants were increased, and the maximal amplitude was reduced.

Many investigators attribute great importance in the pathogenesis of hypocoagulation in thyrotoxicosis to a decrease in the activity of procoagulants and, in particular, of prothrombin. The degree of thyrotoxicosis determines the severity of the hypoprothrombinemia and hypoproconvertinemia [6]. In the present

Department of Pathological Physiology, Central Research Laboratory, I. P. Pavlov First Leningrad Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR A. D. Ado.)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 80, No. 7, pp. 24-26, July, 1975. Original article submitted August 16, 1974.

TABLE 1. Prothrombin and Proconvertin Metabolism in Rats (M ± m)

Clotting factor	Experimental conditions	Index of metabolism			
		K_b (in h^{-1})	$T_{1/2}$ (in h)	A(in %)	L_s (in %/h)
Prothrombin	Control (12)	0,0686±0,00072	10,1±0,08	105,0±3,63	7,24±0,025
	Thyrotoxicosis (9)	0,0742±0,00084	9,35±0,10	81,6±3,91	6,06±0,033
Proconvertin	Control (12)	0,328±0,015	2,12±0,05	96,8±6,52	31,7±0,97
	Thyrotoxicosis (9)	0,438±0,017	1,58±0,06	58,8±4,18	25,8±0,71

Legend. All indices in thyrotoxicosis differed to a statistically significant degree ($P < 0.001$) from the control. Number of animals in parentheses.

experiments with rats with thyrotoxicosis a decrease in the activity and degree of synthesis of prothrombin and, in particular, of proconvertin was observed (Table 1). The breakdown of prothrombin and, in particular, of proconvertin took place more intensively. This was shown by the increase in the breakdown constant and decrease in the biological half-life.

The mechanisms of the fall in activity of the vitamin K-dependent factors in thyrotoxicosis are not yet clear in many respects. There are facts in the literature to show that in thyrotoxicosis the assimilation of vitamin K and sensitivity of the hepatocytes to it are undisturbed [9]. In this disease there is presumably a relative deficiency of vitamin K.

According to Lowenthal and Fischer [15], increased metabolism and increased tone of the sympathetic nervous system may have a significant role in the mechanism of the disturbance of prothrombin metabolism.

In the experiments of Weintraub et al. [17] on dogs, after prolonged administration of D-thyroxine the prothrombin level fell, the breakdown constant increased, and the biological half-life was shortened. Dissociation was found between the calorigenic effect of D-thyroxin and its effect on prothrombin breakdown. On the basis of data in the literature and the results of the present experiments it is considered that increased destruction of these factors plays the principal role in the pathogenesis of the hypoprothrombinemia and hypoproconvertinemia accompanying thyrotoxicosis.

LITERATURE CITED

1. A. K. Gorchakov and R. M. Glants, Vrach. Delo, No. 9, 623 (1946).
2. A. A. Diyarova, in: Proceedings of a Scientific Conference of Azerbaijan Medical Institute [in Russian], Vol. 3, Baku (1972), p. 123.
3. V. A. Zhulkevich, in: Physiology, Biochemistry, and Pathology of the Endocrine System [in Russian], Kiev (1971), p. 40.
4. V. I. Kiyanov and N. N. Petrishchev, in: Hemophilia and Hemorrhages Caused by Disturbance of Blood Clotting [in Russian], Leningrad (1973), p. 96.
5. T. M. Ogonovskii, in: The Blood Clotting System and Fibrinolysis [in Russian], Kiev (1969), p. 366.
6. N. N. Petrishchev, Pat. Fiziol., No. 6, 55 (1973).
7. V. T. Chkhaidze, "Changes in the functional state of blood clotting in patients' thyrotoxic goiter and a method of their correction during preoperative preparation of the patients," Author's Abstract of Candidate's Dissertation, Tbilisi (1971).
8. J. E. Duhart, E. A. Scionico, and E. O. Micheo, Pren. Med. Argent., 57, 1889 (1970).
9. R. Gordin and B. A. Lamberg, Acta Endocrinol. (Copenhagen), 19, 77 (1955).
10. E. Ikkala, A. Eisalo, and O. Heinivaare, Acta Endocrinol. (Copenhagen), 40, 307 (1962).
11. J. Kiczak, M. Eisner, H. Bura, et al., Pol. Arch. Med. Wewnet., 35, 1337 (1965).
12. H. Lasch, K. Mechelke, E. Nasser, et al., Dtsch. Arch. klin. Med., 205, 131 (1958).
13. J. W. Lord and W. W. Andrus, Arch. Surg., 42, 643 (1941).
14. E. A. Loeliger, B. von der Esch, M. J. Mattern, et al., Thrombos. Diathes. Haemorrh. (Stuttgart), 10, 267 (1964).
15. J. Lowenthal and D. M. Fischer, Experientia (Basel), 13, 253 (1957).
16. R. Nagashima, R. A. O'Reilly, and G. Levy, Clin. Pharmacol. Ther., 10, 22 (1969).
17. M. Weintraub, R. T. Breckenridge, and P. F. Griner, J. Lab. Clin. Med., 81, 273 (1973).