The Thyroid and Fibrinolysis

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The profound influence of thyroid dysfunction on metabolic processes is well recognized but only recently has its relation to fibrinolysis been studied. Using a whole blood clot lysis technique, Hume (1965) showed that overall blood fibrinolytic activity is diminished in hyperthyroidism and increased in hypothyroidism ; it was suggested that the increased fibrinolytic activity provides a protective mechanism by which the untreated hypothyroid patient is spared the consequences of occlusive vascular disease. We have extended these findings by measuring the individual components of the fibrinolytic enzyme system in patients with hyperthyroidism and hypothyroidism and by observing the changes in the levels of these components during treatment of both disorders.

Methods

Plasminogen Activator.—Euglobulin clot lysis times were estimated by the method of Nilsson and Olow (1962), and the results were expressed by plotting the values logarithmically against units of fibrinolytic activity (Sherry *et al.*, 1959), 10 units being equated arbitrarily with a lysis time of 50 minutes. Such an assessment of plasminogen activator level has been shown to correlate well with specific assays of plasminogen activator (Fletcher *et al.*, 1964).

Plasma Plasminogen.—This was measured by the caseinolytic method of Remmert and Cohen (1949) as modified by Alkjaersig *et al.* (1959). The results were expressed in Sherry units.

Plasma Fibrinogen.—This was estimated by a modification (Ogston and Ogston, 1966) of the method of Ratnoff and Menzie (1951).

Plasma Antiplasmin.—This was assayed by the technique of Sherry *et al.* (1959) with activator-free plasmin prepared by spontaneous activation of plasminogen (Kabi Pharmaceuticals Ltd.) in 50% glycerol. Results were expressed as percentage inhibition of the standard plasmin preparation.

Plasminogen Activation Inhibitor.—This was measured in serum by the method of Bennett (1967). This technique measures an inhibitor of the activation process distinct from antiplasmin.

Subjects

All 18 hyperthyroid patients studied had an elevated four-hour gland uptake of radioactive iodine (range 44–80%, mean 64% of administered dose). All 16 hypothyroid patients showed depressed serum protein-bound iodine levels (range 1–3 μg./100 ml., mean 1.9 μg./100 ml). Patients with infections, inflammatory conditions, or disorders such as renal disease, which are known to alter the fibrinolytic system, were excluded. Inhibitors were not measured in the first 10 subjects studied. The control subjects were age-matched to the thyroid patients, and comprised members of the medical staff, healthy volunteers, and patients convalescent from a number of minor disorders not known to affect fibrinolysis. No formal studies of thyroid function were carried out on these control subjects, but they were clinically euthyroid and free of symptoms or signs of vascular disease.

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Results

The mean levels and standard deviations of the components of the fibrinolytic system and fibrinogen are presented in the Table.

Plasminogen Activator Levels.—The mean blood activator level of the hyperthyroid group, 1.7 units, was significantly lower than that of the control subjects, 4.7 units, but the hypothyroid patients had a mean activator level, 5.4 units, only slightly greater than the control group, and the difference was not significant.

Inhibitor of Plasminogen Activation.—Patients in the hypothyroid group had a mean inhibitor level of 1.6 units, which is significantly lower than that of the controls, while the hyperthyroid patients had a mean level of 4.3 units, which is significantly higher than that of the euthyroid subjects. This inhibitor does not appear in the euglobulin fraction, and therefore cannot directly influence activator levels as measured by the euglobulin method.

Plasminogen.—The mean plasma plasminogen level in the hypothyroid group was higher than in the control group, and that in the hyperthyroid group was lower than in the control group. Both differences were significant.

Antiplasmin and Fibrinogen.—In contrast with the other components of the fibrinolytic system, antiplasmin levels did not differ in the three groups. Mean fibrinogen levels were greater in both hyperthyroid and hypothyroid groups than in the control subjects, the elevation in the hyperthyroid patients just reaching the 5% significant level, while the elevation in the hypothyroid subjects did not differ significantly from the controls. The difference between the mean fibrinogen levels of the hyperthyroid and hypothyroid groups themselves was not significant.

Levels of Components of Fibrinolytic Enzyme System and Fibrinogen in Hyperthyroid, Euthyroid, and Hypothyroid Subjects

	Hyperthyroid			Sig. of Diff. between Hyperthyroid and Euthyroid Subjects	Euthyroid			Sig. of Diff. between Hypothyroid and Euthyroid Subjects	Hypothyroid		
	No.	Mean Level	S.D.		No.	Mean Level	S.D.		No.	Mean Level	S.D.
Activator (units)	18	1·7	0·8	P < 0·001	34	4·7	1·9	P > 0·1	16	5·4	1·7
Plasminogen (casein units/ml.)	14	3·58	0·56	P < 0·001	34	4·37	0·38	P < 0·01	14	4·70	0·33
Activation inhibitor (units)	13	4·31	0·98	P < 0·001	34	2·42	0·41	P < 0·001	11	1·58	0·39
Antiplasmin (% inhibition)	13	47·3	2·2	P > 0·1	34	46·4	4·9	P > 0·1	11	45·8	5·2
Fibrinogen (mg./100 ml.) ..	18	380	55	P < 0·05	34	347	53	P > 0·1	16	368	72

Serial Studies During Treatment

The serial changes in the components of the fibrinolytic system were measured in one hyperthyroid and one hypothyroid subject during the first six weeks of treatment.

Fig. 1 shows the changes which took place as thyroid overactivity was controlled. Activator levels rose progressively while activation inhibitor fell during the six-week period of observation. Plasminogen, after a very slight fall, rose steadily. All these changes represent a return towards normal levels. Fibrinogen, after a moderate fall during the first two-week period, remained unchanged and antiplasmin levels showed no trend.

Fig. 2 shows the changes which occurred during treatment of the hypothyroid patient with L-thyroxine. During the period of study the observed changes were the reverse of those found during the control of thyroid overactivity, levels again returning toward the mean normal values.

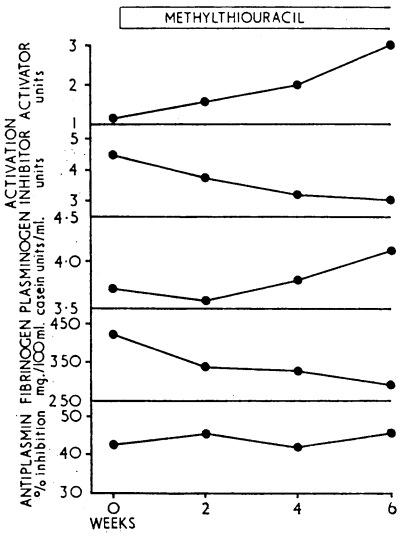

FIG. 1

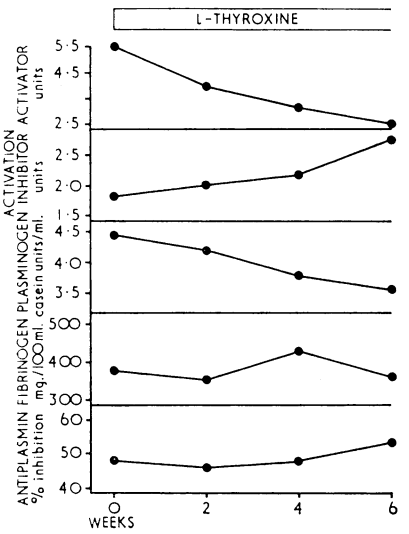

FIG. 2

FIG. 1.—Changes in levels of components of the fibrinolytic system in a hyperthyroid subject during treatment with methylthiouracil. FIG. 2.—Changes in levels of components of the fibrinolytic system in a hypothyroid subject during treatment with L-thyroxine.

Discussion

Altered fibrinolytic activity may be implicated in the formation of intravascular thrombi, and Hume (1965) suggested that the depression of fibrinolytic activity after administration of L-thyroxine might be important in causing acute coronary occlusion in treated hypothyroidism. However, the role of the fibrinolytic system in occlusive vascular disease remains speculative, and it is probable that this system has fundamental functions unrelated to the pathogenesis of coronary artery occlusion. The changes which we have observed in thyroid disorders represent fundamental alterations in the balance of the system. Plasminogen, plasminogen activator, and an inhibitor of activation show changes in opposite directions in hyperthyroid and hypothyroid subjects. In addition, the levels of these factors return to normal as the euthyroid state is restored by treatment with antithyroid drugs or L-thyroxine. The results presented in this study suggest that the fibrinolytic system is a further metabolic process influenced by thyroid hormones. Further, they suggest that the activity of the *normal* thyroid gland may influence physiological changes in fibrinolysis, the regulation of which is as yet not understood.

Summary

Hypothyroidism is associated with an increase in plasminogen, a decrease in an inhibitor of plasminogen activation, and a possible increase in plasminogen activator, whereas hyperthyroid patients show opposite changes in the blood fibrinolytic enzyme system. These changes may play some part in the association between treated hypothyroidism and occlusive coronary disease. More fundamentally they suggest that the thyroid has a regulating influence on fibrinolysis.

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