THYROID FUNCTION IN RATS DURING DEVELOPMENT OF CIRRHOSIS OF THE LIVER

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Changes in absorption of I^{131} and in the biosynthesis of thyroid hormones in the thyroid gland of rats were found during poisoning with the hepatotoxic alkaloid heliotrin. The disturbance of thyroid function is connected to a definite degree with the growth of pathochemical changes in the liver during development of the toxic cirrhosis.

Chemical and experimental investigations have shown disturbances of thyroid function in various forms of liver pathology [2, 3, 15, 16]. However, the results are conflicting and no consistant conclusions can be drawn from them. On the other hand, lesions of the liver are known to be accompanied by disturbances of tissue metabolism of thyroid hormones and by an increase in their blood concentration [5, 6, 12-14, 18].

This paper describes the results of an investigation of thyroid function and hormone formation in rats during the development of cirrhosis of the liver.

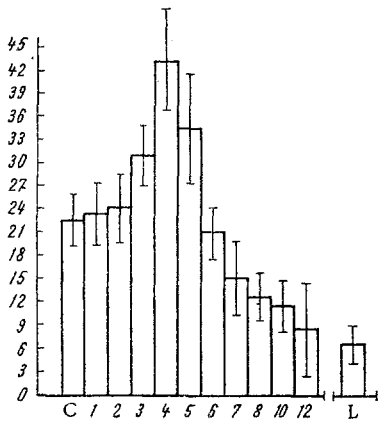

Fig. 1. Absorption of I^{131} by the thyroid gland of experimental rats during development of heliotrin cirrhosis of the liver. C) Control; L) 2 months after last injection of heliotrin. Abscissa, number of injections; ordinate, absorption of I^{131}, in %.

EXPERIMENTAL METHOD

Experiments were carried out on 309 male albino rats weighing initially 130-160 g and kept on the ordinary laboratory diet. Cirrhosis of the liver was induced in these animals by the method described previously [7].

To study the absorption of iodine by the thyroid gland and the biosynthesis of thyroid hormones I^{131} was given in a dose of 0.05 μCi/g body weight. The iodine-absorption capacity and composition of the iodine-containing components were investigated by methods described previously [6, 8].

EXPERIMENTAL RESULTS AND DISCUSSION

Administration of the hepatotoxic poison heliotrin once or twice produced no marked changes in thyroid function, but after the third and fourth injection of the alkaloid the degree of absorption of I^{131} rose sharply (Fig. 1). A similar increase in absorption of iodine by the thyroid gland was obtained by other workers in liver pathology [3, 16]. A particularly noteworthy fact was that even after the sixth injection of heliotrin the thyroid function of some animals still remained high, whereas in most of the experimental rats the fixation of I^{131} showed a

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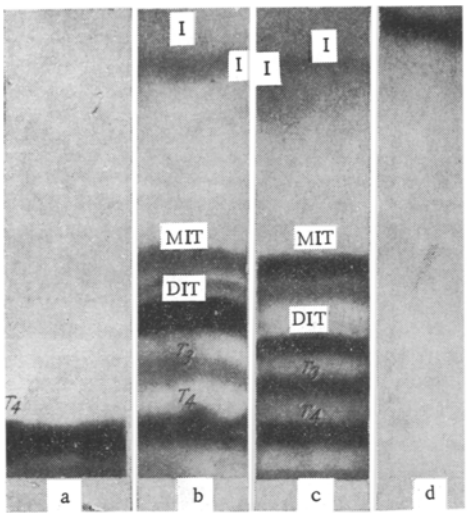

Fig. 2

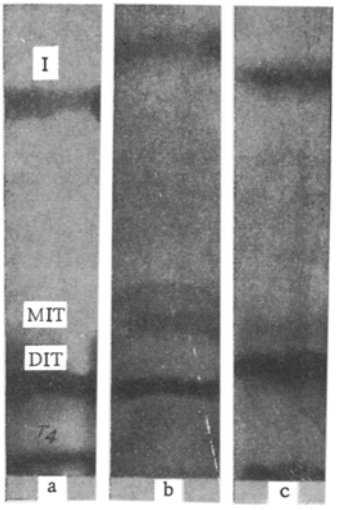

Fig. 3

Fig. 2. Autoradiographs after electrophoresis: a) I^{131}-labeled thyroxine; b) intact rat – butanol extract of thyroid hydrolysate; c) the same experimental rat after receiving four injections of alkaloid; d) standard I^{131}

Fig. 3. Autoradiographs after electrophoresis of butanol extract of thyroid hydrolysate of experimental rats before administration of alkaloid (a), after 12 injections of alkaloid (b), and 2 months after the 12th injection of heliotrin (c; cirrhosis of the liver present).

TABLE 1. Composition of Iodine-Containing Components of the Thyroid Gland in Normal and Experimental Rats (M ± m)

Group of animals	Iodine-containing components			
	iodothyronine ($T_4 + T_3$)	iodotyrosine (DIT + MIT)	inorganic I^{131}	iodotyrosines / iodothyronines
Control (70)	26,2± 1,73	63,1± 2,12	8,1± 0,8	2,41
After 4th injection of heliotrin (46)	38,4± 3,27 $P<0,01$	47,5± 2,38 $P<0,01$	10,2± 1,29 $P<0,01$	1,23
After 12th injection of heliotrin (40)	19,4± 3,43 $P<0,01$	58,2± 2,71 $P<0,01$	20,3± 1,25 $P<0,01$	3,0
Two months after 12th injection of heliotrin (58)	16,9± 1,96 $P<0,01$	68,1± 4,27 $P<0,01$	23,7± 3,4 $P<0,01$	4,1

Legend: T_4 thyroxine, T_3 triiodothyronine, MIT monoiodotyrosine, DIT diiodotyrosine.

Note: Number of animals shown in parentheses.

marked return to normal. Later in the investigation the iodine-absorption capacity of the gland tissue was reduced.

When the rate of hormone synthesis in the thyroid gland was disturbed, changes took place in the concentrations of individual iodine-containing components and in the ratio between the total iodotyrosines and total iodothyronines in the gland (Table 1; Fig. 2).

Determination of the form of iodine in the thyroid tissue by electrophoresis showed a marked increase in the thyroxine and triiodothyronine content in the animals after the fourth injection of the alkaloid at the expense of a decrease in the diiodotyrosine level. The concentration of hormonally-active components (T_3, T_4) in the thyroid gland of rats receiving 10-12 injections of heliotrin, on the other hand, was reduced (Figs. 2 and 3).

These results indicate definite changes in the relative proportion of individual iodine-containing components in the thyroid tissue in heliotrin poisoning. Whereas, at the beginning of the toxic hepatitis a sharp increase in the content of hormonally-active components in the thyroid gland and a decrease in the concentration of iodotyrosines were found in the animals, continued poisoning with hepatotoxic alkaloid and progression of the pathological process in the liver led to a sharp decrease in all indices of thyroid function.

In some rats with marked cirrhosis of the liver virtually no iodothyronines could be detected (Fig. 3b, c). The principal iodine-containing components in the gland were iodotyrosines and inorganic iodine.

It can thus be concluded from the experimental results that the rate of absorption of I^{131} and of hormone synthesis in the thyroid gland is definitely dependent on the pathological state of the liver. Even 2 months after the last injection of heliotrin, a deterioration of thyroid function was observed. This was evidently connected with the fact that the development of pathochemical changes in the liver tissue was still observed even 2-4 months after the end of heliotrin administration [1, 7, 10, 11]. There is evidence in the literature that in liver disease the rate of incorporation of labeled amino acids into thyroid tissue proteins is reduced [4]. There is a noteworthy similarity between the results of investigations [3, 16] of I^{131} absorption in patients with liver disease and the results of the present experiments in the initial stages of heliotrin poisoning in animals. The increase in I^{131} absorption in liver pathology may be connected with general toxic effects on the body and also with the increased intensity of catabolism, in which thyroid hormones participate directly. The possibility of a direct effect of the alkaloid on the thyroid gland itself likewise cannot be ruled out.

This hypothesis is justified if it is remembered that a single injection of a small dose of the alkaloid (5 mg/100 g body weight) in the initial stage of this experiment produced no appreciable change in thyroid function, but subsequent injection of the alkaloid, as a result of an increased concentration of heliotrin in the blood and its accumulation in the organs, especially the thyroid, led to a disturbance of thyroid function. The subsequent decrease in iodine-concentrating power and in the synthesis of hormonally active components in the thyroid gland of the experimental animals may have been the result of the action of the toxic agent, and also of the liver lesion, with a disturbance of iodothyronine metabolism in the body.

It can be concluded from these investigations that the disturbance of thyroid function in heliotrin toxicosis (toxic cirrhosis) is connected to a definite degree with the severity of the pathochemical and pathomorphological changes in the liver.

LITERATURE CITED

1. N. Kh. Abdullaev, Pathochemistry and Pathogenetic Treatment of Chronic Hepatitis and Cirrhosis of the Liver [in Russian], Tashkent (1968).
2. N. Kh. Ageeva, in: Infectious Hepatitis [in Russian], Kiev (1966), p. 174.
3. M. Zukhritdinov, Candidate's Dissertation, Tashkent (1970).
4. R. N. Korotkina, V. N. Nikulin, and A. S. Konnikova, Vopr. Med. Khimii, No. 5, 527 (1968).
5. M. Mirakhmedov, in: The Physiology and Pathology of the Thyroid Gland [in Russian], Tashkent (1966), p. 26.
6. M. Mirakhmedov and R. Shakirova, in: Problems in Medical Chemistry and the Action of Physiologically Active Substances [in Russian], Tashkent (1970), p. 108.
7. Ya. Kh. Turakulov, Biochemistry of the Thyroid Hormones [in Russian], Tashkent (1962).
8. Ya. Kh. Turakulov and M. Mirakhmedov, Proceedings of the First Conference of Biochemists of the Republics of Central Asia and Kazakhstan [in Russian], Tashkent (1967), p. 315.
9. M. N. Khanin, Med. Zh. Uzbekistana, No. 8, 28 (1968).
10. R. M. Shakirova, N. I. Rasulev, and M. Mirakhmedov, in: Current Problems in Local Pathology [in Russian], Tashkent (1969), p. 120.
11. S. M. Milcu, L. Vailler, and E. Kostiner, Probl. Éndokrinol., No. 5, 24 (1958).
12. T. Beraud, Acta Endocrinol. (Copenhagen), Suppl. 55, 41 (1960).
13. J. W. Cowan and S. Mardossioni, Endocrinology, 70, 1023 (1966).
14. P. J. Davis, Am. J. Med., 40, 918 (1966).
15. D. M. Kidd and E. B. Mann, J. Clin. Invest., 30, 874 (1951).
16. K. Kowalewski, Acta Endocrinol. (Copenhagen), 24, 20 (1957).
17. R. Mulluer, C. C. Brausch, E. Z. Hirsch, et al., J. Clin. Endocrinol., 14, 1284 (1954).
18. B. R. Scazziga, T. Beraud, and A. Vannotti, Schweiz. Med. Wschr., 85, 471 (1956).