RATE OF CHOLESTEROL SYNTHESIS IN HYPO- AND HYPERTHYROID RATS*

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Recently it was found in this laboratory that the hyperthyroid rat excretes far more cholesterol in his bile than the normal animal, whereas the hypothyroid rat has a considerably smaller daily output than the normal animal (1). This finding suggested that the rate of cholesterol synthesis was increased in the hyperthyroid and decreased in the hypothyroid state. Findings, however, such as the reciprocal relationship between thyroid activity and serum cholesterol level (2), the protection afforded by cholesterol against thyroid toxicity (3, 4), and the protective effect of thyroid against experimental atherosclerosis (5, 6) do not naturally lead to the thought that hyperthyroidism increases the rate of cholesterol synthesis. In the present study, tritium has been used to obtain data on the turnover rate of cholesterol in normal, hypo- and hyperthyroid animals. The results show a more rapid turnover in the hyperthyroid animal, and a slower turnover in the hypothyroid animal, as compared with normal controls.

EXPERIMENTAL

Data concerning the rate of cholesterol turnover were obtained on four groups of male rats of the Long-Evans strain. One group was fed powdered thyroid substance (0.3 per cent of the diet) for 14 days; at the time of the experiment these animals were 10 weeks old. A second group was fed thiouracil (0.3 per cent of the diet) for 98 days; at the time of the experiment this group was 20 weeks old. Two control groups of 9 week and 18 week old rats, respectively were fed stock diet. Dietary supplements administered as above have been shown (7, 8) to induce hyperthyroidism and hypothyroidism, respectively, in rats. The activity, food consumption, weight changes, general condition, and behavior of our groups of rats confirmed this observation.

The weight gain was largest in the control group and least in the hyperthyroid group. The rats receiving thiouracil had a retarded growth and decreased activity; those given thyroid substance exhibited hyperactivity, marked tremor, tachycardia, and polyphagia.

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TABLE I

Rate of Cholesterol Turnover in the Rat with Thyroid Derangement

Rat No.	Age of rat	Weight of rat	Thyroid function	Total cholesterol in viscera	Weight of viscera	Cholesterol specific activity	$T_{\frac{1}{2}}$*
	wks.	*gms.*		*mg.*	*gms.*	*μc./gm.*	*days*
704	9	250	Normal	51.6	33.0	0.37	34.6
1251		275		58.0	44.0	0.59	19.8
1201		250		73.4	39.1	0.72	17.3
1289		240		65.4	35.7	0.73	17.3
745		273		71.2	40.6	0.85	13.8
Mean		257		63.9	38.5	0.65	20.6
S.E. mean				±4.1	±1.9	±0.08	±3.6
1248	10	196	Hyperthyroid	71.2	29.1	1.10	10.7
802		190		69.4	29.9	1.60	7.3
1736		200		69.2	32.0	2.04	6.3
1725		150		84.0	27.4	3.48	2.9
1717		222		79.2	32.8	1.47	7.7
Mean		192		74.6	30.2	1.94	7.0
S.E. mean				±2.7	±1.1	±0.41	±2.0
50	18	326	Normal	41.8	52.4	0.81	14.9
66		297		93.6	45.4	0.35	34.8
74		288		56.2	40.4	0.45	26.9
77		350		22.8	52.4	0.62	19.6
95		317		78.8	52.8	0.35	34.8
Mean		316		62.6	48.7	0.52	26.2
S.E. mean				±12.8	±2.5	±0.09	±4.0
725	20	290	Hypothyroid	68.0	39.9	0.18	69.3
795		375		52.8	45.9	0.22	58.0
1265		250		59.4	34.5	0.27	43.0
1256		350		70.2	47.4	0.27	43.0
749		310		68.0	42.1	0.32	38.5
Mean		315		63.7	42.0	0.25	50.4
S.E. mean				±3.3	±2.3	±0.02	±5.7

* The half-time of turnover of visceral cholesterol was calculated using the formula $N = C(1 - e^{-kt})$ and assuming an equilibrium state during the period of the labelling experiment, where N = cholesterol specific activity; $C = \frac{1}{2}$ body water specific activity, measured as in references 9 and 10, or 17.8 μc./gm.; $t = 1$ day; $k = \frac{0.693.}{T_{\frac{1}{2}}}$

Histological changes in the thyroid glands from each group resembled those described by Karp and Stetten (8). Liver slices respiring in air in the Warburg respirometer showed QO_2

values markedly increased in the hyperthyroid livers and decreased from normal in the hypothyroid livers.[1]

At the end of the feeding period each rat then received 0.122 cc. tritium water (S.A. = 20.5 μc./cc.) per 100 gm. of body weight by intravenous injection. Food and water were withheld thereafter during the entire experimental period. 24 hours after injection, the animals were bled and the abdominal and thoracic organs were collected. Both the blood and organs of each rat were combined and were hydrolyzed with 30 per cent KOH in 50 per cent ethanol. The non-saponifiable material was extracted with ether. The cholesterol was precipitated with digitonin and the specific activity determined as described previously (9, 10).

RESULTS

The data are summarized in Table I. The mean specific activity of visceral cholesterol is greater in the hyperthyroid rats than in normal animals and conversely is lower in the hypothyroid group. The visceral cholesterol content varies relatively little among the different groups. Therefore, the difference in specific activities indicates an increase in the rate of cholesterol synthesis (and destruction) in the hyperthyroid animals and a decrease in this rate in the hypothyroid animals.

The mean half-time of turnover for visceral cholesterol in normal rats under the condition of this study is 20.6 days for the 9 week old animals and 26.2 days for the 18 week old animals; for the hyperthyroid animals 7.0 days, and for the hypothyroid animals 50.4 days.

DISCUSSION

The data show a more rapid rate of cholesterol synthesis in the hyperthyroid rat than in the normal rat, and a slower rate in the hypothyroid animal. Since the dose of tritium water was administered on the basis of total body weight, the degree of labelling depended upon the percentage of body weight constituted by body water. The results obtained could not have been due to differences in total body water among animals in different thyroid states since body water has been reported to increase with increase in metabolic rate (11). Such a change would dilute the tritium water and thus show a falsely low turnover rate in hyperthyroidism, rather than the high rate found. Thiocyanate space, partly dependent upon body water, also has been found to increase in hyperthyroidism and to decrease in hypothyroidism (12).

The direct relationship found between the thyroid activity, rate of cholesterol synthesis, and rate of biliary excretion of cholesterol (1) furnishes additional evidence for the usefulness of biliary cholesterol output as an indicator of the rate of cholesterol synthesis (13).

Our conclusion that administration of thyroid substance increases the rate of cholesterol metabolism is in conflict with that of Fleischmann and Shumaker (14). These authors measured blood and total body cholesterol in thyroid

[1] We are indebted to Dr. Shirley M. St. George for the respirometer determinations.

derangement in rats and rabbits and, finding no parallelism between concentrations of body cholesterol and cholesterol in serum, concluded that thyroid had no over-all effect on cholesterol metabolism. The tracer technique used in our work, however, permits the demonstration of changes in turnover rate of visceral and blood cholesterol regardless of the relative cholesterol concentrations.

SUMMARY

The rate of cholesterol synthesis, measured by the rate of incorporation of tritium from body water into the cholesterol molecule, was found to be greater than normal in the hyperthyroid rat and below normal in the hypothyroid rat.

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