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Kenneth A. Woeber, … , Sidney H. Ingbar, Kenneth Sterling

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Research Article

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The Peripheral Metabolism of Triiodothyronine in Normal Subjects and in Patients with Hyperthyroidism

KENNETH A. WOEBER, RICHARD J. SOBEL, SIDNEY H. INGBAR, and KENNETH STERLING

From the Thorndike Memorial Laboratory, Second and Fourth (Harvard) Medical Services, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts; and the Protein Research Laboratory, Bronx Veterans Administration Hospital, and the Department of Pathology, Columbia University College of Physicians and Surgeons, New York 10032

ABSTRACT In order to assess the contribution of 3.3′,5-triiodo-L-thyronine (T_3) to overall thyroid hormone economy, conjoint measurements of the kinetics of peripheral T_3 metabolism and the total concentration of T_3 in serum were made in a group of normal subjects and in a group of patients with hyperthyroid Graves' disease. As judged from the disappearance of trichloroacetic acid–precipitable ^{131}I from serum after a single intravenous dose of labeled T_3, the following mean values were obtained in the normal subjects: volume of distribution, 43 liters or 0.62 liter/kg; fractional turnover rate, 52% per 24 hr; clearance rate, 22.3 liters/24 hr; and absolute disposal rate, 60 μg/24 hr. In the patients with untreated hyperthyroidism, values for all these functions were greatly increased. After treatment, the volume of T_3 distribution returned to normal but the fractional turnover rate remained abnormally rapid.

INTRODUCTION

The increasing evidence that 3,3′,5-triiodo-L-thyronine (T_3) is important relative to L-thyroxine (T_4) in normal thyroid hormone economy and in iodine metabolism makes essential an appreciation of the quantitative aspects of the kinetics of peripheral T_3 metabolism. Previously reported data are relatively scant and, in some respects, conflicting (1–8). Although some data concerning the total concentration of T_3 in serum are available (9–11), conjoint measurements of T_3 concentration and of the kinetics of T_3 turnover in the same individual, to make possible measurements of the absolute rate of disposal of hormone, have not been made. Data are particularly scant concerning the peripheral metabolism of T_3 in patients with hyperthyroidism (5, 12), a disorder in which recent measurements of the total concentration of T_3 in serum suggest that this hormone may play a preponderant role. Accordingly, we undertook to study the peripheral metabolism of T_3 and its absolute rate of disposal in a group of normal subjects and in a group of patients with hyperthyroid Graves' disease.

METHODS

Studies of the peripheral metabolism of ^{131}I-labeled T_3 were carried out in seven normal subjects and in seven patients with hyperthyroid Graves' disease. Of the latter, four were restudied after 2–8½ months of treatment. Table I lists the clinical and laboratory data obtained in the hyperthyroid patients.

Each individual was given an intravenous injection of 50 μCi (approximately 2 μg) of sterile ^{131}I-labeled T_3[1] in a 1% (w/v) solution of human serum albumin. Significant thyroidal recycling of inorganic ^{131}I liberated by the peripheral degradation of labeled hormone was prevented by the administration of Lugol's iodine (2 drops every 8 hr). In the hyperthyroid patients, large doses of methimazole (30 mg every 6 hr) were given in addition to Lugol's iodine. Throughout the study, 12-hr urine collections were made and samples of blood were drawn twice daily, usually at 12-hr intervals.

The concentration of trichloroacetic acid (TCA)–precipitable ^{131}I in serum was determined as follows. To 1 ml of serum was added carrier iodide and a few milligrams of propylthiouracil, followed by 1 ml of cold 20% TCA. The resulting precipitate was washed twice with cold 5% TCA,

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[1] Obtained from The Radiochemical Centre, Amersham, England. At the time of injection, this material was approximately 95% pure, as judged by filter paper chromatography, iodide being the sole detectable contaminant.

TABLE I

Clinical and Laboratory Data Obtained in the Patients with Hyperthyroid Graves' Disease

Patient	Age, Sex	Clinical features	State	Treatment	Serum BEI	BMR	Weight
	yr				*μg/100 ml*	*%*	*kg*
1	37, M	Diffuse goiter and ophthalmopathy	Thyrotoxic		>20	+84	52
			Treated	Methimazole for 5½ months	2.0	−13	66
2	26, F	Diffuse goiter and ophthalmopathy	Thyrotoxic		11.4	+67	40
			Treated	Methimazole for 8½ months	4.4	−6	47
3*	23, F	Diffuse goiter and ophthalmopathy	Thyrotoxic		4.2	+49	48
			Treated	Methimazole for 2 months	1.2	−4	54
4	37, F	Diffuse goiter	Thyrotoxic		7.4		58
			Treated	Methimazole for 7 months	2.6		66
5	30, F	Diffuse goiter	Thyrotoxic		8.4		48
6	60, F	Multinodular goiter	Thyrotoxic		7.0	+90	61
7	32, F	Diffuse goiter	Thyrotoxic		11.0		45

BMR, basal metabolic rate.

* Although this patient had normal values for serum BEI and protein-bound iodine (PBI) (6.0, 6.8 μg/100 ml), she was clinically very toxic and had a serum T_3 value of 928 ng/100 ml, which is more than three times the mean value in our normal subjects.

dissolved in 2 N sodium hydroxide, and made up to a standard volume for counting. Sufficient counts were obtained to reduce the probable counting error at 72 hr to a maximum of 5%.

In each study, the declining concentration of TCA-precipitable ^{131}I in serum was plotted as a function of time. The regression coefficient for that part of the curve which appeared to conform to a single exponential function was calculated by the method of least squares and was used to calculate the fractional rate of T_3 turnover. The volume of distribution of T_3 was calculated by a method previously employed for assessing the volume of distribution of T_4 (13). This method is designed to correct for the disproportionate loss of administered ^{131}I before attainment of distribution equilibrium. The rate of clearance of T_3 was calculated as the product of the volume of distribution and the fractional rate of turnover. Data were not sufficiently numerous to permit analysis according to multicompartmental models.

The total concentration of T_3 in serum was measured according to the method of Sterling, Bellabarba, Newman, and Brenner (10). The absolute rate of T_3 disposal was calculated as the product of the total concentration of T_3 in serum and the rate of T_3 clearance. The concentration of butanol-extractable iodine (BEI) in serum was measured by the method of Benotti and Pino (14).[2]

RESULTS

In the normal subjects and the hyperthyroid patients, only 64% and 61% respectively of the ^{131}I in serum was precipitable with TCA 12 hr after injection of the ^{131}I-labeled T_3; this proportion remained essentially constant through the next 48 hr of study, averaging at 72 hr 68% in the normal subjects and 71% in the hyperthyroid patients.

[2] Performed by the Boston Medical Laboratory, Boston, Mass.

Normal subjects. The volume of distribution and fractional rate of turnover of T_3 after attainment of distribution equilibrium were calculated from the data obtained during the period from 24 to 72 hr after administration of the ^{131}I-labeled T_3. Verification that distribution equilibrium of the residual labeled T_3 had been attained by 24 hr was obtained as follows. In each subject, values for TCA-precipitable ^{131}I in serum during the period from 24 to 72 hr after injection of the labeled T_3 were expressed as a per cent of the 24 hr value. The pooled data for the entire group were then used to calculate, by the method of least squares, regression coefficients for the periods 24–48 and 24–72 hr. After 72 hr, the values for TCA-precipitable ^{131}I in serum were considered to be unreliable because of the low counting rates and the contribution thereto of the iodoprotein that arises as a product of T_3 degradation (6, 15). As depicted in Fig. 1, the fractional turnover rates calculated from the regression coefficients for the periods 24–48 and 24–72 hr agreed closely. This indicated that a single exponential rate of disappearance had been present during this time; hence, distribution equilibrium of the residual labeled T_3 had been attained. The kinetic values derived from the data obtained in each subject during the period from 24 to 72 hr are presented in Table II. The mean value for the volume of T_3 distribution was 43 ±2 liters (mean ±SE) or 0.62 ±0.03 liter/kg, and for the fractional rate of T_3 turnover, 52 ±5% per 24 hr. The calculated rates of T_3 clearance therefore averaged 22.3 ±2.1 liters/24 hr. Values for the total concentration of T_3 in serum averaged 273 ±23 ng/100 ml, and for the absolute rate of

T_3 disposal, 60 ±7 μg/24 hr. Calculated values for the fraction of injected ^{131}I ultimately appearing in the urine (urinary maximum) averaged 78 ±5% of the administered dose.

Hyperthyroid patients. In the patients with untreated hyperthyroidism, the individual disappearance curves of TCA-precipitable ^{131}I in serum drawn from data obtained during the period from 24 to 72 hr appeared to deviate from a single exponential function. Consequently, as in the normal subjects, the data were pooled and regression coefficients for the periods 24–48 and 24–72 hr were calculated (Fig. 1). The resulting pooled disappearance curve appeared to conform to a single exponential function from 24 to 48 hr, but thereafter the rate of disappearance of TCA-precipitable ^{131}I decreased. During the untreated thyrotoxic state, therefore, fractional rates of T_3 turnover were determined from the individual data obtained from 24 to 48 hr. In the studies performed after treatment, the calculated regression coefficients for the periods 24–48 and 24–72 hr agreed closely. Nevertheless, both because of the relatively poor correlation of the 60 and 72 hr points with the calculated regression line and for purposes of comparison with the untreated thyrotoxic state, fractional rates of T_3 turnover were determined from the individual data obtained only during the period from 24 to 48 hr.

Table II summarizes the data obtained. The mean value for the volume of T_3 distribution in the patients with untreated hyperthyroidism was 45 ±5 liters or 0.91 ±0.13 liter/kg. The value related to body weight was significantly greater than that in the normal subjects ($P < 0.001$). Treatment was followed by a decrease in the volume of T_3 distribution; this decrease was significant statistically, as judged from the paired t test ($P < 0.01$). In the untreated patients, the mean value for the fractional rate of T_3 turnover was 84 ±6% per 24 hr. This value was significantly greater than that obtained in the normal subjects ($P < 0.01$) and did not change appreciably after treatment. The mean value for the calculated rate of T_3 clearance in the untreated patients was 36.7 ±3.7 liters/24 hr. This value was also significantly greater than that obtained in the normal subjects ($P < 0.01$). In the four patients studied before and after treatment, T_3 clearance rate decreased during treatment in all with the mean clearance rate changing from 38.7 to 24.5 liters/24 hr. This difference was statistically significant when corrected for body weight ($P < 0.05$). Values for the rate of T_3 clearance in patients with treated hyperthyroidism were very similar to and did not differ significantly from those in the normal group, regardless of whether or not they were expressed in relation to body weight. In the untreated patients, the mean value for the total concentration of

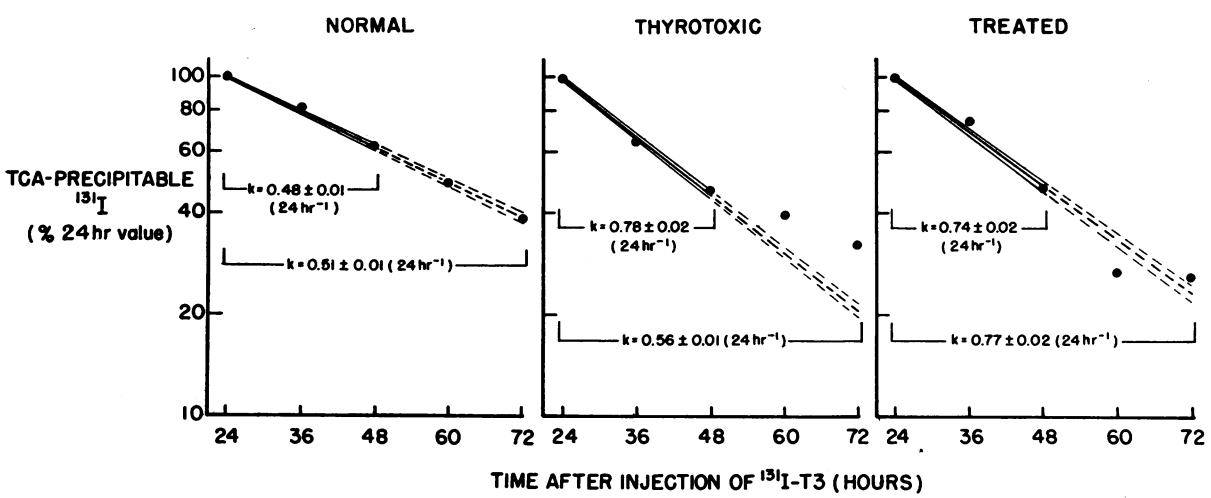

FIGURE 1 Pooled curves for the disappearance of trichloroacetic acid (TCA)-precipitable ^{131}I from serum after the administration of labeled 3,3',5-triiodo-L-thyronine (T_3) to normal subjects and to patients with untreated and treated hyperthyroid Graves' disease. In each curve, the individual points are the mean of values obtained in individual subjects, expressed as a per cent of their individual 24-hr values. In the normal subjects, the concentration of TCA-precipitable ^{131}I in serum at 24 hr averaged 1.32% administered dose/liter, with a range of 1.13–1.76. The corresponding values in the patients with untreated and treated hyperthyroid Graves' disease were 0.96 (range, 0.59–1.31) and 1.33 (range, 1.09–1.85), respectively. The values for fractional turnover rate (k) shown represent the mean ±SE calculated by the method of least squares. The values shown are similar but not identical to those in Table II and the text since they were derived from the pooled data for each group.

T_3 in serum was 912 ±94 ng/100 ml, and the absolute rates of T_3 disposal averaged 336 ±48 μg/24 hr, a value significantly greater than that found in the normal subjects ($P < 0.001$). In the treated patients, attempts were made to measure the total concentration of T_3 in serum, but a transient technical problem exhausted the small supply of serum. The values for urinary maximum varied widely in the untreated patients, did not differ significantly from those obtained in the normal subjects, and did not change in a consistent manner after treatment.

DISCUSSION

The increasing awareness of the likelihood that T_3 plays an important role relative to T_4 in overall thyroid hormone economy makes an appreciation of the kinetics of peripheral T_3 metabolism essential. Some data concerning this topic are available, but they are relatively scant and certain inconsistencies exist among them (1–8). Much of this conflict doubtless stems from difficulties in assessing accurately the distribution and turnover of the labeled hormone which result ultimately from its rapid peripheral metabolism. The first problem con-

TABLE II

The Kinetics of the Peripheral Metabolism of 3,3',5-Triiodo-L-Thyronine (T_3) in Normal Subjects and in Patients with Hyperthyroid Graves' Disease Before and After Treatment

Subject	Age, Sex	Body weight	Volume of distribution		Fractional turnover rate	Clearance rate	Serum T_3 concentration	Absolute disposal rate	Urinary maximum
	yr	*kg*	*liters*	*liters/kg*	*%/24 hr*	*liters/24 hr*	*ng/100 ml*	*μg T_3/24 hr*	*% dose*
Normal									
1	31, M	68	43	0.63	67	28.8	230	66	83
2	30, M	75	46	0.61	60	27.6	266	73	81
3	38, M	74	43	0.58	40	17.2			91
4	58, M	53	34	0.64	45	15.3	222	34	54
5	39, M	57	41	0.72	68	27.9			70
6	38, M	60	42	0.70	49	20.6	342	70	79
7	37, F	119	55	0.46	34	18.7	306	57	86
Mean		72	43	0.62	52	22.3	273	60	78
SE		8	2	0.03	5	2.1	23	7	5
Untreated hyperthyroidism									
1	37, M	52	46	0.88	93	42.8	1200	514	81
2	26, F	40	42	1.05	82	34.4	1248	429	100
3	23, F	48	43	0.90	106	45.6	928	423	30
4	37, F	58	47	0.81	68	32.0	668	214	90
5	30, F	48	26	0.54	98	25.5	988	252	56
6	60, F	61	38	0.62	69	26.2	679	178	60
7	32, F	45	72	1.60	70	50.4	675	340	67
Mean		50	45	0.91*	84‡	36.7‡	912*	336*	69
SE		3	5	0.13	6	3.7	94	48	11
Treated hyperthyroidism									
1 a§	37, M	66	32	0.48	94	30.1			72
2 a	26, F	47	38	0.81	57	21.7			97
3 a	23, F	54	25	0.46	76	19.0			85
4 a	37, F	66	35	0.53	78	27.3			65
Mean		58	32	0.57‖	76¶	24.5			80
SE		5	3	0.08	8	2.5			7

* Vs. normal subjects, $P < 0.001$.

‡ Vs. normal subjects, $P < 0.01$.

§ The letter "a" indicates that the patient is the same as the patient indicated by the same number in the untreated hyperthyroid group.

‖ Vs. thyrotoxic patients by paired t test, $P < 0.01$.

¶ Vs. normal subjects, $P < 0.05$.

cerns the appearance in serum of labeled products of T_3 degradation which tend to obscure the primary T_3 disappearance curve. The second problem concerns the question of whether distribution equilibrium has been attained during that period when accurate measurements of the concentration of residual labeled T_3 in serum are still possible.

The present study has demonstrated that radioiodide is a major degradative contaminant of the residual labeled T_3, constituting about one-third of the total radioactivity in serum during the period from 12 to 72 hr. Consequently, all the present data for serum represent values for TCA-precipitable, rather than total, ^{131}I. A second product of T_3 degradation is an iodoprotein which is butanol-insoluble and TCA-precipitable (6, 15). Since this material appears to turn over at a slower rate than T_3, the question must be raised as to whether it has materially influenced the present estimates of the distribution and turnover of T_3, which are based upon measurements of TCA-precipitable ^{131}I. Two lines of evidence indicate that this is not the case in the normal subjects. The first is the close concordance that we have observed between the calculated regression coefficients for the periods 24–48 and 24–72 hr. Had the butanol-insoluble material exerted a significant influence, the regression coefficient calculated from the pooled data obtained from 24 to 72 hr would have been significantly smaller than the corresponding value for the 24 to 48 hr period. The second is the fact that, with one exception (1), previously reported values for the fractional rate of T_3 turnover, regardless of whether corrections were made for the butanol-insoluble radioiodine, agree remarkably well with those presented here (2–8). This close agreement is all the more remarkable when considered in light of the fact that in one study (3) the values obtained were derived from whole body counting whereas in the present study as well as the remaining previous studies (2, 4–8), the values were derived from data analyzed according to a single compartmental model, indicating that the error introduced by this type of analysis is minimal.

In the normal subjects, concordance of the calculated regression coefficients for the 24–48 and 24–72 hr periods also indicated that the administered labeled T_3 had attained virtually complete distribution equilibrium by 24 hr. Stronger evidence that distribution equilibrium of labeled T_3 is attained by 24 hr is provided by data obtained by the method of Nicoloff and Dowling (16). Nicoloff has found that when a dose of radioiodine-labeled T_3 is administered and allowed to equilibrate and is then followed by a second pulse of T_3 labeled with a different radioisotope of iodine, the ratio of the two isotopes in the urine becomes constant between 12 and 17 hr.[3] This period is the time required for the second pulse to attain distribution equilibrium.

Reported values for the volume of distribution of T_3 vary widely, but in general they are several-fold larger than those for T_4, probably owing to the much weaker binding of T_3 than of T_4 in serum (17). With respect to T_3, mean values as low as 18.1 and 22.8 liters have been reported (4, 5). In contrast are the present values which averaged 43 liters, and those reported by Surks and Oppenheimer which averaged 38.1 liters (6). In one remaining study, values for the volume of T_3 distribution were derived from whole body counting and averaged 31 liters (3); however, if this value were corrected for the proportion of TCA-soluble radioactivity that we have found, a value of approximately 46 liters would result. We are unable to account for the discrepancies between these two groups of observations.

The present study appears to be the first in which conjoint measurements of the rate of T_3 clearance and the total concentration of T_3 within the pool, and hence the absolute rate of T_3 disposal, have been made in the same individual. In the normal subjects, values for the absolute rate of T_3 disposal averaged 60 $\mu g/24$ hr, a figure not greatly different from the approximately 80 μg of T_4 which is turned over daily in the normal individual (13). It should not be concluded, however, that these values necessarily represent the relative rates of secretion of the two hormones from the thyroid gland since recent evidence indicates that a substantial quantity of T_3 arises from T_4, at least when the latter is given orally (18). For the same reason, it is not justifiable to draw inferences concerning the relative metabolic contributions of the T_4 and T_3 secreted by the thyroid gland.

The problems encountered in analyzing curves of the disappearance of T_3 from serum were accentuated in the patients with untreated hyperthyroidism. Unlike the case in the normal subjects, curves for the disappearance of TCA-precipitable ^{131}I from serum did not conform to a single exponential function after 48 hr. This might be due to the greater relative contribution of the butanol-insoluble ^{131}I to the total TCA-precipitable radioactivity. Hence, it was necessary to estimate the fractional rate of T_3 turnover from data obtained during the period from 24 to 48 hr after administration of the labeled T_3. Although estimates of the fractional rate of turnover based on such a short period of observation are less than ideal, the very rapid rate of turnover tends to increase their accuracy since one half-life could be observed during the 24 hr period.

In the present study, the fractional rate of T_3 turnover was greatly increased in the hyperthyroid patients,

[3] Nicoloff, J. T. Personal communication.

a change similar to that previously reported for T_4 (13). This cannot be ascribed to inclusion of the butanol-insoluble ^{131}I in the TCA-precipitable radioactivity in serum since this would retard rather than accelerate the disappearance curve. The increase in the fractional rate of turnover is in all likelihood owing to an increase in the activity of intracellular mechanisms for T_3 metabolism. It cannot be ascribed solely to hypermetabolism since it tends to persist after the hyperthyroidism has been treated. Furthermore, it cannot be ascribed to an increase in the serum T_4 concentration per se since an acute increase in serum T_4 concentration induced by a T_4 load decreases rather than increases the fractional rate of T_3 turnover (19). In untreated hyperthyroidism, the volume of T_3 distribution was also increased when related to body weight. This increase was, in all likelihood, owing to an increased degree of saturation of thyroxine-binding globulin (TBG) resulting from the increased total concentrations of T_4 and T_3 in serum and the decreased binding capacity of TBG (20, 21). As a result of these changes, the calculated rate of T_3 clearance was greatly increased. A very pronounced increase in the total concentration of T_3 in serum was also seen. Relative to normal values, this increase was disproportionately greater than that for T_4, as judged from measurements of the BEI, in the same patients. The absolute daily rate of T_3 disposal averaged 336 μg, a value more than five times the normal. It is uncertain whether this increase in daily disposal is relatively greater than that observed in the case of T_4, and hence, whether T_3 contributes disproportionately to the maintenance of the hyperthyroid state. This question could best be answered by studying the simultaneous turnover of both hormones in a single group of patients.

After treatment, the volume of T_3 distribution returned to normal, reflecting, in all likelihood, the combination of a decrease in the total concentrations of T_4 and T_3 and an increase in the binding capacity of TBG in serum (21). By contrast, the increase in the fractional rate of turnover persisted after treatment, despite the attainment of a normal metabolic state. This persistent abnormality in the peripheral metabolism of T_3 is reminiscent of that previously observed for T_4 in treated hyperthyroidism (22, 23) and indicates that the acceleration of hormonal turnover in hyperthyroidism is not due solely to the hypermetabolism per se.

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