Effects of Replacement Doses of Sodium-L-Thyroxine on the Peripheral Metabolism of Thyroxine and Triiodothyronine in Man

LEWIS E. BRAVERMAN, APOSTOLOS VAGENAKIS, PATRICIA DOWNS, ANGELA E. FOSTER, KENNETH STERLING, and SIDNEY H. INGBAR

From the St. Elizabeth's Hospital, Boston 02135 and Department of Medicine, Tufts Medical School, Boston 02111, the Thorndike Memorial Laboratory and the Harvard Medical Service, Boston 02115; Boston City Hospital, Boston 02118; and the Department of Medicine, Harvard Medical School, Boston, Massachusetts 02115; the Protein Research Laboratory, Bronx Veterans Administration Hospital, Bronx, New York 10468; and the Department of Medicine, Columbia University College of Physicians and Surgeons, New York 10027

ABSTRACT Studies of the effect of L-thyroxine administration (0.3 mg daily for 7–9 wk) on the peripheral metabolism of ^{131}I-labeled triiodothyronine (T_3) and ^{125}I-labeled thyroxine (T_4) and on the concentration and binding of T_4 and T_3 in serum were carried out in 11 euthyroid female subjects. Administration of L-thyroxine led to consistent increases in serum T_3 concentration (137 vs. 197 ng/100 ml), T_3 distribution space (39.3 vs. 51.7 liters), T_3 clearance rate (22.9 vs. 30.6 liters/day) and absolute T_3 disposal rate (30 vs. 58 μg/day), but no change in apparent fractional turnover rate (60.3 vs. 60.6%/day). The proportion and absolute concentration of free T_3 also increased during L-thyroxine administration. Increases in serum total T_4 concentration (7.3 vs. 12.8 μg/100 ml) and in both the proportion and absolute concentration of free thyroxine also occurred. In five of the subjects, the kinetics of peripheral T_4 turnover were simultaneously determined and a consistent increase in fractional turnover rate (9.7 vs. 14.2%/day), clearance rate (0.84 vs. 1.37 liters/day), and absolute disposal rate (64.2 vs. 185.0 μg/day) occurred during L-thyroxine administration. Despite these increases in the serum concentration and daily disposal rate of both T_4 and T_3, the patients were not clinically thyrotoxic. However, basal metabolic rate (BMR) values were marginally elevated and, as in frank thyrotoxicosis, T_4-binding capacities of thyroxine-binding globulin (TBG) and thyroxine-binding prealbumin (TBPA) reduced, suggesting that subclinical thyrotoxicosis was present. Thus, the often recommended replacement dose of 0.3 mg L-thyroxine daily may be greater than that required to achieve the euthyroid state.

The studies have also provided additional evidence of the peripheral conversion of T_4 to T_3 in man and have permitted the calculation that approximately one-third of exogenously administered T_4 underwent deiodination to form T_3. To the extent that a similar fractional conversion occurs in the normal state, it can be calculated that a major fraction of the T_3 in serum derives from the peripheral deiodination of T_4 and that only a lesser fraction derives from direct secretion by the thyroid gland.

INTRODUCTION

In 1970, studies from our laboratories provided the first conclusive evidence that thyroxine (T_4)[1] is converted

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[1] *Abbreviations used in this paper:* ETT_4, extrathyroidal T_4 pool; $\%FT_3$, per cent free T_3; $\%FT_4$, per cent free T_4; SSKI, saturated solution of potassium iodide; TBG, thyroxine-binding globulin; TBG_{cap}, measurements of T_4-binding capacities by TBG; TBPA, thyroxine-binding prealbumin; $TBPA_{cap}$, measurements of T_4-binding capacities by TBPA; T_3, triiodothyronine; T_3DS, T_3 distribution space; T_3(RIA), T_3 measured by radioimmunoassay; T_4, thyroxine; T_4(D), T_4 measured by displacement; T_4DS, T_4 distribution space; TSH, thyroid-stimulating hormone.

to triiodothyronine (T_3) in the peripheral tissues of man (1). This conclusion has since been repeatedly confirmed (2–5), and conversion of T_4 to T_3 has been demonstrated, in addition, in the intact rat (6) and in isolated human cells in vitro (7–9). Our conclusion was based in part on the finding that athyreotic patients receiving exogenous L-thyroxine therapy had in their serum concentrations of T_3 far greater than those which would have been expected on the basis of contamination of the administered T_4 by T_3 (1). An unexplained feature of this study was the finding that although these patients did not appear thyrotoxic by clinical criteria, serum T_4 concentrations were well into the range found in spontaneously thyrotoxic patients, and serum T_3 concentrations also appeared distinctly elevated by the methods of analysis then available.

In an effort to examine this apparent discrepancy, to examine the conjointly-measured kinetics of peripheral T_4 and T_3 metabolism in patients receiving L-thyroxine, and to assign quantitative dimensions to the extent of peripheral conversion of T_4 to T_3, studies were conducted in which the effects of L-thyroxine on the peripheral metabolism of T_4 and T_3 in euthyroid individuals were assessed. A portion of the studies has been the subject of a preliminary communication (10).

METHODS

Studies were conducted in 11 normal female volunteers ranging from 22 to 54 yr in age. Studies of the peripheral metabolism of T_3 were carried out in all 11 before and after a 7–9 wk period of L-thyroxine administration (0.3 mg/day orally [P.O.]). In five, studies of the peripheral metabolism of T_4 were conducted concurrently with those of T_3.

Studies of the peripheral metabolism of T_3 were made using ^{131}I-labeled T_3.[2] After its receipt from a commercial source, labeled T_3 was mixed with sterile human serum albumin (final concentration 4 g/100 ml) and was dialyzed against 2 liters of sterile physiological saline solution at 4°C for 2 h. As judged by chromatography in two solvent systems in which iodide and T_4 or T_3 were well separated (butanol-ethanol ammonia, 5:1:2; butanol-dioxane ammonia, 4:1:5), this procedure decreased the contaminating [^{131}I]iodide from approximately 1.6 to approximately 0.6%. Approximately 1% of the ^{131}I migrated as T_4, and this was unchanged by dialysis. Dialyzed solutions were passed through a Millipore filter before their administration to patients. Patients received a single intravenous (i.v.) injection of 100 μCi (4.6–8.5 μg) of ^{131}I-labeled T_3. Blood samples were drawn at 24-h and at 12-h intervals thereafter for the next 2 days. Sera were separated and were treated with Iobeads to remove labeled inorganic iodide.[3]

Studies of the peripheral metabolism of T_4 were conducted with ^{125}I-labeled hormone that was not predialyzed but which was diluted with sterile human serum albumin (final concentration 4 g/100 ml) and passed through a Millipore filter before administration to the patients. Chromatographic analysis revealed approximately 2% of the radioactivity to be in the form of iodide and none in the form of T_3. Each of the five patients in whom such studies were carried out received a single i.v. injection of 40 μCi (approximately 4 μg) of ^{125}I-labeled hormone administered immediately after the injection of ^{131}I-labeled T_3. In these patients, in addition to the samples of serum obtained for studies of T_3 metabolism, specimens were obtained daily for 6 more days.

2 ml samples of serum were counted for ^{131}I and ^{125}I in a scintillation spectrometer, correction being made when indicated for the ^{131}I counts detected in the ^{125}I spectrum. Radioactivity in serum samples was expressed in relation to that present in appropriately diluted samples of the administered dose. Calculations of the kinetics of T_3 metabolism were based on data obtained in samples drawn from 24 to 72 h after administration of [^{131}I]T_3 and, in the case of T_4, samples drawn from 2 to 9 days after [^{125}I]T_4 administration. Fractional turnover rates were calculated by the method of least squares, and volumes of T_4 and T_3 distribution were determined by extrapolation of the calculated regression curves to zero time.

In order to prevent the thyroidal uptake of inorganic ^{131}I or ^{125}I generated by the peripheral deiodination of T_4 or T_3 during the control period, five drops of saturated solution of potassium iodide (SSKI) were given orally each day. SSKI was also administered during the second turnover study, although thyroidal iodine uptake had been shown to be suppressed by the exogenous hormone administered.

Samples of serum from each turnover study were pooled and analyzed in duplicate for T_4 concentration (T_4[D])[4] by a modification of the method of Murphy and Pattee (12) and for T_3 concentration (T_3[RIA]) by a modification of the radioimmunoassay of Gharib, Mayberry, and Ryan (13), using antibody kindly provided by these authors. By the method employed, normal values in 26 subjects averaged 150±25 ng/100 ml (mean ±SD). Measurements of T_4-binding by TBG (TBG_{cap}) and TBPA ($TBPA_{cap}$) and of the per cent of free T_4 (%FT_4) and of free T_3 (%FT_3) were carried out in sera obtained on two separate days during each turnover study. Absolute concentrations of FT_4 and FT_3 were calculated as the product of the per cent and total concentration of T_4 and T_3 in serum, respectively. For each function studied, analyses of all four sera from each subject were carried out on the same day. TBG_{cap} and $TBPA_{cap}$ were measured by reverse flow and conventional filter paper electrophoresis, respectively, using glycine acetate buffer, pH 8.6, account being taken of the endogenous serum T_4 concentration (14). %FT_4 and %FT_3 were measured in triplicate by a modification of the equilibrium dialysis technique of Ingbar, Braverman, Dawber, and Lee (15).

Statistical analyses were conducted according to methods described by Snedecor (16).

[2] ^{131}I-labeled T_3 and ^{125}I-labeled T_4 were obtained from Abbott Laboratories, Chicago, Ill.

[3] Control studies have revealed that treatment of serum with Iobeads for 5 min removes more than 99% of inorganic ^{131}I and less than 1% of labeled iodothyronines.

[4] Abbreviations used to denote the serum concentrations of T_4 and T_3, the proportions and absolute concentrations of T_4 and T_3 and the T_4-binding capacities of TBG and TBPA are those recently adopted by the American Thyroid Association (11).

TABLE I

*Effect of L-thyroxine Administration on the Concentration and Binding of T_4 and T_3 in the Serum of Normal Subjects**

Subject	Age	Treatment	Serum T_3	PFT_3	AFT_3	Serum T_4	PFT_4	AFT_4	TBG	TBPA
			ng/100 ml	%	*ng/100 ml*	*ug/100 ml*	%	*ng/100 ml*	*ug T_4/100* ml	*ug T_4/100* ml
1	47	Control	132	0.16	0.21	7.0	0.018	1.3	26.0	240
		LT_4‡	208	0.21	0.44	11.5	0.025	2.8	23.0	196
2	30	Control	100	0.16	0.16	6.5	0.018	1.2	23.5	205
		LT_4	160	0.22	0.36	12.0	0.025	3.0	16.5	173
3	49	Control	144	0.19	0.27	5.5	0.018	1.0	17.0	208
		LT_4	184	0.26	0.48	11.0	0.026	2.8	15.5	187
4	33	Control	168	0.16	0.28	7.5	0.018	1.4	22.0	169
		LT_4	212	0.21	0.44	13.5	0.022	2.9	19.0	155
5	25	Control	120	0.17	0.21	7.0	0.019	1.3	23.5	207
		LT_4	200	0.24	0.49	13.0	0.027	3.6	20.0	176
6	38	Control	132	0.19	0.25	9.0	0.018	1.6	21.0	269
		LT_4	200	0.23	0.46	12.5	0.022	2.7	21.0	226
7	22	Control	140	0.17	0.24	6.5	0.018	1.1	23.0	228
		LT_4	156	0.22	0.34	12.0	0.022	2.7	19.0	204
8	54	Control	156	0.18	0.28	8.0	0.017	1.4	19.0	241
		LT_4	208	0.25	0.52	15.0	0.031	4.6	16.5	197
9	26	Control	152	0.19	0.29	8.5	0.018	1.5	21.5	231
		LT_4	192	0.21	0.41	13.5	0.023	3.2	21.5	187
10	37	Control	116	0.19	0.23	7.5	0.019	1.4	21.0	236
		LT_4	152	0.24	0.37	13.0	0.024	3.1	21.0	190
11	29	Control	152	0.17	0.27	7.5	0.016	1.2	23.5	229
		LT_4	232	0.23	0.53	14.0	0.021	2.9	19.0	182
Mean ±SD		Control	137±20	0.18±0.01	0.24±0.03	7.3±1.0	0.018±0.001	1.3±0.2	21.9±2.5	223±26
		LT_4	191±25	0.23±0.02	0.44±0.06	12.8±1.1	0.024±0.003	3.1±0.6	19.3±2.4	188±18
P value (paired *t* test)			<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.005	0.001

* PFT_3, proportion of free T_3; AFT_3, absolute concentration of free T_3; PFT_4, proportion of free T_4; AFT_4, absolute concentration of free T_4.

‡ Each subject received 0.3 mg L-thyroxine P.O. daily for 7–9 wk.

RESULTS

Concentration and binding of T_4 in serum (Table I). Before administration of L-thyroxine, T_4(D) in the 11 patients studied averaged 7.3±1.0 μg/100 ml (mean± SD); $\%FT_4$, 0.018±0.001%; and FT_4, 1.29±0.19 ng/100 ml. All values were within the normal range. Also normal were values for TBG_{cap} (21.9±2.4 μg/100 ml) and $TBPA_{cap}$ (223±26 μg/100 ml). During L-thyroxine administration, mean T_4(D) increased to 12.8±1.0 μg/100 ml and $\%FT_4$ to an average of 0.024±0.003%. Values for FT_4 were strikingly increased, averaging 3.1±0.5 ng/100 ml, an increase of 141% from control values. TBG_{cap} (19.3±2.4 μg T_4/100 ml) and $TBPA_{cap}$ (188± 18 μg T_4/100 ml) were decreased slightly, but significantly, from control values, ($P < 0.005$ and $P < 0.001$, respectively).

Peripheral metabolism of T_4 (Table II). In the five subjects in whom the appropriate studies were performed, indices of the peripheral metabolism of T_4 during control periods were within the normal range. During the administration of L-thyroxine, T_4 distribution space (T_4DS) was not significantly changed (8.7±0.8 liters vs. 9.7±1.0 liters), but the fractional rate of turnover (K) increased from a mean of 9.7±0.8%/day to a mean of 14.2±1.8%/day. As a result, the rate of total T_4 clearance (C) increased from a mean of 0.84±0.09 to a mean of 1.37±0.10 liters/day. The content of the extrathyroidal T_4 pool (ETT_4) increased during the administration of L-thyroxine by an average of 100%. Total daily disposal of T_4 increased markedly from a mean of 64.2± 9.6 to a mean of 185±23 μg T_4/day.

Concentration and binding of T_3 in serum (Table I). During administration of L-thyroxine, values of T_3(RIA) increased from a control mean of 137±20 to a mean of 191±25 ng/100 ml. $\%FT_3$, which averaged 0.18±0.01 in the control period, increased to a mean of 0.23±0.02%. Values for FT_3 were about doubled, increasing from a mean of 0.24±0.03 to a mean of 0.44±0.06 ng/100 ml.

Peripheral metabolism of T_3 (Table III). Before L-thyroxine administration, indices of the peripheral

TABLE II

*Effect of L-thyroxine Administration on the Peripheral Metabolism of T_4**

Subject	Age	Treatment	Serum T_4	T_4DS	K	ETT_4	C	D
			ug/100 ml	*liters*	*%/day*	*ug*	*liters/day*	*ug/day*
7	22	Control	6.5	8.6	10.2	559	0.88	57
		LT_4‡	12.0	9.3	13.3	1,116	1.23	147
8	54	Control	8.0	7.8	9.0	624	0.70	56
		LT_4	15.0	10.2	13.8	1,530	1.40	210
9	26	Control	8.5	9.7	9.7	824	0.94	80
		LT_4	13.5	9.1	15.2	1,228	1.38	186
10	37	Control	7.5	8.1	10.8	607	0.87	65
		LT_4	13.0	8.9	16.9	1,157	1.50	195
11	29	Control	7.5	9.5	8.9	712	0.84	63
		LT_4	14.0	11.3	12.0	1,582	1.35	189
Mean ±SD		Control	7.6±0.7	8.7±0.8	9.7±0.8	665±104	0.84±0.09	64.2±9.6
		LT_4	13.5±1.2	9.7±1.0	14.2±1.8	1,322±217	1.37±0.10	185.0±23.0
P value (paired *t* test)			<0.001	NS	<0.005	<0.005	<0.005	<0.001

* T_4DS, T_4 distribution space; K, fractional rate of T_4 turnover; ETT_4, extrathyroidal T_4 pool; C, rate of total T_4 clearance; D, total daily disposal of T_4.

‡ Each subject received 0.3 mg L-thyroxine P.O. daily for 7–9 wk.

TABLE III

*Effect of L-thyroxine Administration on the Peripheral Metabolism of T_3**

Subject	Age	Treatment	Serum T_3	T_3DS	K	ETT_3	C	D
			ng/100 ml	*liters*	*%/day*	*ug*	*liters/day*	*ug/day*
1	47	Control	132	34.0	64.0	45	21.7	29
		LT_4‡	208	39.8	70.7	83	28.3	59
2	30	Control	100	35.5	61.6	36	21.8	22
		LT_4	160	42.6	67.2	68	28.6	46
3	49	Control	144	32.1	65.8	46	21.1	30
		LT_4	184	60.7	58.1	111	35.2	64
4	33	Control	168	30.0	70.6	50	21.2	35
		LT_4	212	38.7	67.4	82	26.1	55
5	25	Control	120	27.2	72.4	33	19.7	24
		LT_4	200	47.9	67.8	96	32.5	66
6	38	Control	132	41.4	76.8	55	31.8	42
		LT_4	200	50.1	76.8	100	38.5	77
7	22	Control	140	50.4	46.7	71	23.5	33
		LT_4	156	59.2	47.3	92	28.0	43
8	54	Control	156	39.0	43.4	61	16.9	26
		LT_4	208	51.7	49.4	107	25.5	53
9	26	Control	152	58.8	44.4	89	26.1	39
		LT_4	192	59.9	47.2	115	28.3	54
10	37	Control	116	49.4	51.3	57	25.3	29
		LT_4	152	69.3	48.2	105	33.4	51
11	29	Control	152	34.7	66.2	53	23.0	35
		LT_4	232	48.9	66.9	113	32.7	76
Mean ±SD		Control	137±20	39.3±9.7	60.3±11.8	54±16	22.9±3.8	30±6
		LT_4	191±25	51.7±9.6	60.6±10.9	97±15	30.6±4.0	58±11
P value (paired *t* test)			<0.001	<0.001	NS	<0.001	<0.001	<0.001

* T_3DS, T_3 distribution space; K, fractional rate of T_3 turnover; ETT_3, extrathyroidal T_3 pool; C, rate of total T_3 clearance; D, total daily disposal of T_4.

‡ Each subject received 0.3 mg L-thyroxine P.O. daily for 7–9 wk.

metabolism of T_3 were similar to those previously reported for euthyroid adults (17–20). The T_3 distribution space (T_3DS) averaged 39.3±9.7 liters; the fractional turnover rate, 60.3±11.8%/day; and the total T_3 clearance rate, 22.9±3.8 liter/day. The extrathyroidal pool of T_3 averaged 54±15 μg and daily T_3 disposal, 30±6 μg/day. With the exception of the fractional rate of T_3 turnover (60.6±10.9%/day), which appeared to be unchanged, all other functions cited above increased significantly ($P < 0.001$) during L-thyroxine administration. Serum T_3 concentration increased by an average of 40%, T_3DS by an average of 32%, total T_3 clearance by 34%, and total daily disposal of T_3 by 93%.

Conversion of T_4 to T_3. On the likely assumption that thyroidal secretion of T_3 during administration of L-thyroxine was negligible, values for T_4 and T_3 disposal during this period could be employed to calculate the proportion of T_4 converted to T_3. Individual values for daily T_3 disposal were multiplied by a factor of 1.193 to ascertain the molar equivalent quantity of T_4. The resulting values were divided by the corresponding values for daily T_4 disposal to obtain the proportion of T_4 converted to T_3. These ranged from 30.2 to 48.0%, averaging 35.7±7.2.

Proportionate conversion of T_4 to T_3 during control periods could not be estimated, since it was impossible to distinguish T_3 arising from deiodination of T_4 from that secreted directly by the thyroid gland. The latter function could be estimated if it were assumed that values for the proportionate conversion of T_4 to T_3 obtained in each patient during L-thyroxine administration also pertained during control periods. To obtain such estimates, control values for daily T_4 disposal were multiplied by the value for percentage conversion of T_4 to T_3 during L-thyroxine administration. The resulting product, representing the micrograms of T_4 estimated to undergo monodeiodination daily, was divided by 1.193 to obtain the molar equivalent quantity of T_3. The resulting value for the micrograms of T_3 generated from T_4 daily was then divided by the total T_3 disposal rate, providing an estimate of the fraction of total daily T_3 disposal derived from conversion of T_4. Values of this estimate ranged between 51 and 72%, averaging 59±8%.

DISCUSSION

In previous studies, we have demonstrated that athyreotic patients receiving traditional replacement doses of L-thyroxine (0.3 mg daily) have in their serum substantial concentrations of T_3, indicating appreciable conversion of T_4 to T_3 in the peripheral tissues of man (1). This conclusion, which has received strong additional support (2–5) and has been extended to the rat (6), has raised inter-related questions as to the origin of the T_3 found in serum, the nature of the thyroidal secretory product, and the ultimately active form of the thyroid hormone. Central to each of these questions is the actual extent of peripheral conversion of T_4 to T_3; however, such could not be determined from our previous studies in athyreotic patients, since the rates of turnover and clearance of T_4 and T_3 were not ascertained.

The present studies were undertaken to explore this and other questions concerning thyroid hormone physiology in patients receiving replacement doses of L-thyroxine. Studies were conducted in euthyroid subjects so that absolute rates of T_4 and T_3 turnover and disposal during L-thyroxine administration could be compared with those obtained in the basal state. Moreover, in view of the marked suppression of thyroid function produced by L-thyroxine administration, as evidenced by decreases in 24 h thyroid ^{131}I uptakes from a mean of 28 to a mean of 3%, T_3 present in serum during this period can be considered to have arisen largely or entirely from extrathyroidal sources, permitting estimates of the rate of T_4 to T_3 conversion.

The normal or increased concentrations of T_3 found in serum of the present patients during L-thyroxine administration have confirmed the findings obtained in the anatomically athyreotic patients reported earlier.[5] In addition, in the five patients in whom concurrent studies of T_4 and T_3 disposal were carried out, the extent to which T_4 was converted to T_3 during L-thyroxine administration could be estimated, since thyroidal secretion of T_3 could be presumed to be negligible. Calculated values for the per cent of T_4 converted to T_3 ranged from 30.2 to 48.0, averaging 35.7±7.2. These results agree closely with those obtained by Pittman, Chambers, and Read (2) based on studies with [^{14}C]T_4. They also agree rather well with those obtained by Surks, Schadlow, and Oppenheimer (4) in similar studies of four athyreotic patients treated with L-thyroxine. They reported that approximately half of the T_4 deiodinated was converted to T_3. Since about 20% of T_4 is metabolized by nondeiodinative pathways, a value of approximately 40% overall T_4 to T_3 conversion is obtained. Similar estimates have been obtained by Cullen, Burger, Woeber, and Ingbar in untreated euthyroid subjects by a differ-

[5] When, in 1969 and 1970, the present studies were actually performed, analyses for serum T_3 were conducted by displacement analysis (21), a method now known to yield values substantially and possibly erroneously higher than those obtained by radioimmunoassay. At that time, it was beginning to be evident that this was the case. Therefore, samples of serum were kept continuously frozen until clarification of methodological problems was achieved and a radioimmunoassay for T_3 was established in the authors' laboratories. The values herein presented are the results of the latter analyses, and differ substantially in a quantitative sense from those presented in our preliminary report (10).

ent technique in which conversion is calculated from the concurrently measured clearance rates of [^{125}I]T_4 and [^{131}I]T_3 and equilibrium values for the ratio of [^{125}I]T_3/[^{125}I]T_4 in serum.[6]

The finding that about one-third or one-half of the peripheral T_4 is metabolized to T_3, together with the two- or threefold greater metabolic potency of T_3 than T_4, has led to the suggestion that virtually all of the metabolic activity of T_4 resides in the T_3 generated from it and that T_4 is merely a prohormone for T_3. Several considerations prompt caution in this interpretation, however. All estimates of T_4 to T_3 conversion to date have been what might be termed "plasma conversion rates," since they are based on concentrations and disappearance rates for T_3 in plasma. They do not reflect any T_3 generated from T_4 that is locally degraded or excreted without entering the plasma. The extent to which true conversion rates exceed plasma conversion rates is unknown. Moreover, it is unknown whether T_3 generated and metabolized locally has any metabolic action and, if it does, how its intrinsic potency compares with that of T_3 that enters the cell from the extracellular fluid. In view of these uncertainties, conclusions concerning the intrinsic potency of T_4 based on the fractional conversion of T_4 to T_3 and the overall potency of the two in the whole animal would seem premature.

Plasma conversion rates do bear directly, however, on the proportion of total daily disposal of T_3 that is derived from the monodeiodination of T_4, when disposal rates are based upon plasma disappearance rates and plasma concentrations of the two hormones. Thus, the plasma T_4 to T_3 conversion rate times the daily disposal of T_4, when corrected for the lower molecular weight of T_3, will indicate the quantity of T_3 in plasma derived from T_4 daily. The present estimates of conversion rates derived from data obtained while patients were receiving L-thyroxine, when applied to the present conjoint measurements of T_4 and T_3 disposal in the basal state, would indicate that approximately 60% of daily T_3 disposal (and of plasma T_3 concentration) derives from the monodeiodination of T_4.

At the time these studies were carried out, the effect of labeled iodoproteins arising from T_3 deiodination on the apparent disappearance from the serum of the labeled T_3 was just becoming evident (22). Hence, separation of labeled iodoproteins from the labeled T_3 remaining in serum was not carried out, although removal of labeled iodide was. The question arises, therefore, as to the extent to which the measured kinetics of T_3 metabolism were influenced by failure to exclude iodoprotein. It is most unlikely that this influenced the results of control studies materially, since values for T_3DS and fractional turnover rate did not differ substantially from those obtained when labeled iodoprotein is excluded (19). This is doubtless the result of the fact that in normal individuals iodoprotein contributes but little to the plasma radioactivity during the 24 to 72 h period in which measurements are made (17). The effect of iodoprotein on measurements made during L-thyroxine administration is less certain, however. To the extent that the clearance of T_3 is increased, lower values for plasma labeled T_3 concentration at any point in time would be expected. In addition, to the extent that increased clearance of T_3 resulted from increased deiodination, a more rapid generation of iodoprotein would be expected. Together, these effects would yield a slower apparent rate of decline of T_3 concentration in plasma than is actually the case. This effect was probably operative in the present studies, and may have resulted in the lack of change in values for T_3 fractional turnover rate during L-thyroxine administration.

It is substantially less clear, however, what the effect of iodoprotein on calculated values for T_3DS would be. If, as previous studies would suggest (17), iodoprotein is but a small percentage of total organically-bound radioiodine at 24 h after labeled T_3 administration and is a progressively larger proportion at later times, then the zero time intercept of the least squares regression curve based on total organic radioiodine would be erroneously low and values for T_3DS erroneously high. This spurious increase in T_3DS would tend to reduce, but not eliminate, the error in calculated values for T_3 clearance caused by underestimation of the fractional turnover rate. The magnitude of such an error is difficult to estimate, however, since there have apparently been no studies in which sera freed of radioiodide were studied with and without removal of iodoprotein to ascertain the magnitude of the effect of including iodoprotein on calculated values of T_3DS and fractional turnover rate.[7] It is apparent, however, that, to the extent that T_3 clearance was underestimated, then the percentage peripheral conversion of T_4 to T_3 would have been proportionately underestimated and calculated values for the thyroidal secretion of T_3 too high. The close agreement between values for T_4 to T_3 conversion found in the present studies and those found in the studies of Pittman, Surks, and Cullen and their respective co-

[6] Cullen, M. J., A. Burger, K. A. Woeber, and S. H. Ingbar. Unpublished observations.

[7] Nicoloff, Low, Dussault, and Fisher (19) have published curves depicting plasma disappearance of total radioactivity and iodothyronine radioactivity after administration of labeled T_3. From these curves it is quite clear that values for both T_3DS and k would be greatly reduced if total plasma radioactivity, rather than iodothyronine activity, were considered. However, since inorganic iodide comprises approximately 40% of total plasma radioactivity after a dose of labeled T_3 (17), much of the apparent decrease in T_3DS can be ascribed to inclusion of iodide, rather than iodoprotein.

workers (2, 4) in which iodoprotein was eliminated from serum before analysis, would suggest, however, that the error introduced by our failure to eliminate iodoproteins was small.

Until recently, it has been assumed that adequate replacement therapy with L-thyroxine would require doses sufficient to establish values for serum T_4 concentration above the normal range, since the metabolic contribution normally provided by T_3 was presumed to be lacking (23–27). With the demonstration of peripheral T_4 to T_3 conversion, however, the rationale for this approach no longer seemed valid, provided that the rate of production of T_3 was physiologically significant. Although our earlier studies of athyreotic patients receiving L-thyroxine therapy revealed normal or increased concentrations of serum T_3, production rates could not be inferred, since peripheral T_3 turnover was not studied under these circumstances.

The present studies have shown, however, that euthyroid patients receiving 0.3 mg L-thyroxine daily undergo at least a doubling in the daily disposal rate for T_3 and a trebling in that for T_4, as compared to the production and disposal rates sustained by their endogenous thyroid function. It would appear, therefore, that the conventional replacement dose of 0.3 mg of L-thyroxine daily does provide both T_4 and T_3 in excess of normal physiological requirements. One might then expect patients receiving this dose to manifest signs of thyroid hormone excess. Frank thyrotoxicosis would be unlikely in view of the fact that quantities of T_4 and T_3 provided by 0.3 mg L-thyroxine daily, although greater than normal, were far less than the usual production rates of T_4 and T_3 in hyperthyroid patients, as judged from reports in the literature (17, 19, 28–33). The present patients manifested no clinical signs of thyrotoxicosis. On the other hand, several findings provide suggestive though not conclusive evidence that they were mildly hypermetabolic. First, in six of the eight patients, values of the BMR (+8–+15%) during suppressive therapy were above the normal range for our laboratory (−15–+5%); however, in none were pretreatment values available.

Second, TBG_{cap} and $TBPA_{cap}$ decreased during L-thyroxine therapy, changes reminiscent of those found in patients with spontaneous thyrotoxicosis (34, 35). The few available data of other workers also supports the conclusion that 0.3 mg of L-thyroxine daily may often be an excessive replacement dose. Most authors emphasize the difficulty of selecting between 0.2 mg daily and 0.3 mg daily on the basis of subjective findings alone (26, 27, 36–38); however, when objective criteria such as BMR have been assessed, doses of 0.2 mg daily frequently seem sufficient (36, 39). The most telling evidence, however, is the recent finding of Cotton, Gorham, and Mayberry (40) that in patients with hypothyroidism doses of 0.2 mg daily usually suffice to restore serum thyroid-stimulating hormone (TSH) concentration to normal.

The apparent physiological (and clinical) tolerance of euthyroid young adults to slight or moderate excesses of thyroid hormone is well-known, particularly from instances where the hormone is administered in an effort to treat obesity. In addition, patients with autonomous thyroid nodules and complete suppression of paranodular thyroid function often are not detectably thyrotoxic, although it is most unlikely that the nodule is secreting quantities of hormone precisely equivalent to physiological needs. Such apparent resistance to mild excesses of thyroid hormone may merely bespeak the insensitivity of clinical and biochemical indices of thyroid hormone excess currently available. It might also reflect enhanced activity of pathways for hormonal metabolism that are purely degradative or excretory, i.e., that forestall hormonal action. Finally, to the extent that hormonal excess is judged to exist on the basis of increased serum concentration or disposal rate of T_4, the validity of such judgments will depend upon the extent to which T_4 proves to have a metabolic action independent of its conversion T_3. All of these considerations, and perhaps others, await clarification.

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