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Research Article

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Inhibition of Thyrotropin Response to Thyrotropin-Releasing Hormone by Small Quantities of Thyroid Hormones

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ABSTRACT Inhibition of thyrotropin (TSH) release by chronic treatment with small quantities of triiodothyronine (T_3) and thyroxine (T_4) was evaluated by determining the serum TSH response to thyrotropin-releasing hormone (TRH) in normal subjects and hypothyroid patients. Response to TRH was determined before treatment and after each dosage of a synthetic combination of $T_3 + T_4$ had been given for 3–4 wk.

Treatment of eight normal subjects with 15 μg T_3 + 60 μg T_4 reduced the maximum increase in serum TSH above baseline (maximum ΔTSH) by 76% in response to 400 μg TRH and by 87% in response to 25 μg TRH. The average serum T_3 level during a 24 hr period in normal subjects who had been taking 15 μg T_3 + 60 μg T_4 for 3–4 wk was 129±10 ng/100 ml (mean ±SEM), well within the normal range, 70–150 ng/100 ml, although higher than the pretreatment level, 98±7 ng/100 ml. The average serum T_4 level was unchanged from the pretreatment level. Treatment of the same subjects with 30 μg T_3 + 120 μg T_4 reduced the maximum ΔTSH further.

Six patients with primary hypothyroidism were treated, sequentially, with 15 + 60, 22.5 + 90, and 30 μg T_3 + 120 μg T_4. For each patient there was one increase in dosage of 7.5 μg T_3 + 30 μg T_4 which abruptly converted a maximum ΔTSH that was greater than, or at the upper limit of, normal to one that was subnormal. Concurrent with these six abrupt changes in TSH response, the mean serum T_3 level increased only from 105±5 to 129± 9 ng/100 ml, and the mean serum T_4 level increased only from 4.9±0.8 to 6.3±0.5 μg/100 ml.

These data demonstrate the extreme sensitivity of TRH-induced TSH release to inhibition by the chronic administration of quantities of $T_3 + T_4$ which do not raise serum T_3 and T_4 levels above the normal ranges.

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INTRODUCTION

The objective of this study was to quantitate the degree to which small quantities of triiodothyronine (T_3)[1] and thyroxine (T_4) can inhibit the release of thyrotropin (TSH) in man. Although the ability of exogenous T_3 and T_4 to reduce the elevated serum TSH levels in patients with primary hypothyroidism to within the normal range has been well documented (1, 2), determination of the quantity of T_3 and/or T_4 necessary to suppress serum TSH from normal to below normal levels had been difficult previously because of the inability to distinguish between normal and low serum TSH levels by the TSH immunoassay.

The recent availability of synthetic thyrotropin-releasing hormone (TRH), which stimulates TSH release in normal man (3–5), makes possible the determination of the quantity of T_3 and/or T_4 necessary to inhibit TSH release to a greater extent than it is inhibited normally; greater than normal inhibition should be manifest, presumably, by a subnormal serum TSH response to exogenous TRH. It already has been demonstrated, in fact,, that in overt hyperthyroidism TSH release is inhibited to the extent that the administration of TRH in usually effective doses produces virtually no rise in serum TSH (6, 7). The inhibitory effect of smaller elevations of serum T_3 and T_4 levels on TSH release was determined in the present study by measuring the serum TSH response to the acute i.v. administration of TRH to normal subjects and patients with primary hypothyroidism who were treated chronically with small dosages of a synthetic combination of $T_3 + T_4$. Concomitant measurement of serum T_3 and T_4 levels at the time of the TRH tests demonstrated the serum levels of these hormones necessary to produce inhibition of the TSH response to TRH.

[1] *Abbreviations used in this paper:* PBI, protein-bound iodine; T_3, triiodothyronine; T_4, thyroxine, TRH, thyrotropin-releasing hormone; TSH, thyrotropin.

TABLE I

Characteristics of Normal Subjects and Patients with Primary Hypothyroidism

Subject	Age	Sex	Etiology of hypothyroidism
	yr		
Normal subjects			
N. B.	29	M	
J. B.	21	M	
T. D.	26	M	
J. D.	22	M	
B. F.	21	M	
J. M.	21	M	
D. O.	24	M	
J. R.	24	M	
Patients with primary hypothyroidism			
M. B.	65	F	idiopathic
M. C.	80	F	idiopathic
P. D.	46	M	Hashimoto's thyroiditis
A. F.	58	M	idiopathic
E. G.	62	F	idiopathic
D. G.	48	F	idiopathic
L. H.	64	M	post-^{131}I therapy for Graves' disease
R. N.	32	M	idiopathic
E. R.	54	F	postthyroidectomy for Graves' disease
R. S.	28	F	idiopathic
M. Y.	38	F	idiopathic

METHODS

Eight normal subjects and eleven patients with primary hypothyroidism gave informed consent to receive TRH. Table I lists their clinical characteristics. A patient was defined as having primary hypothyroidism when his serum T_4 level was below the normal range and his serum TSH was above the normal range. (Normal values are given below.)

Six additional normal subjects participated in the study by taking $T_3 + T_4$ (see below) but did not receive TRH. None of the normal subjects or patients took any medication known, or suspected, to affect thyroid hormone economy during the study, with the exception of the study medication. No normal subject had a history of thyroid disease, and each had normal initial serum T_3, T_4, and TSH levels.

A synthetic combination of $T_3 + T_4$ (liotrix, Warner-Chilcott Laboratories, Morris Plains, N. J.) was the only thyroid medication used. The dosages were 15 μg $T_3 + 60$ μg T_4, 22.5 μg $T_3 + 90$ μg T_4, and 30 μg $T_3 + 120$ μg T_4, henceforth referred to as 15 + 60, 22.5 + 90, and 30 + 120.

The serum TSH response to the rapid (10–15 sec) i.v. injection of synthetic TRH (Abbott Laboratories, North Chicago, Ill.) was tested in each normal subject and hypothyroid patient both before and during $T_3 + T_4$ treatment. The TRH injection and blood sampling techniques have been described (8). Before the injection of TRH blood was drawn for the determination of serum T_3 and T_4 concentrations, as well as for the determination of serum TSH concentration. The standard TRH dose was 400 μg, since this is the minimum dose that produces the maximum TSH response in normal subjects (8). The normal subjects, after the initial TRH test, took 15 + 60 daily for 3–4 wk before being tested again with TRH. After the second TRH test, the subjects took 30 + 120 for 3–4 wk before being tested for a third time. The hypothyroid patients followed the same protocol, except that they took the 22.5 + 90 dosage, as well as the other dosages, and had a TRH test on this dosage. Six of the normal subjects were tested with 25 μg of TRH, as well as with 400 μg TRH, while still taking 15 + 60. In these cases the second TRH test was at least 3 days after the first. The $T_3 + T_4$ medication was taken once a day, in the morning, and the TRH tests were always done 24 hr after the last dose at any given dosage. No measurements of either TSH response to TRH or serum T_3 or T_4 levels were made until each dosage of $T_3 + T_4$ had been taken for 3–4 wk, because available evidence suggests that serum TSH levels in primary hypothyroid patients do not equilibrate until thyroid replacement medication has been given for at least that long (2).

Serum TSH (9) and serum T_3 (10) concentrations were measured by immunoassay. The anti-T_3 serum used in the T_3 immunoassay was different from the one described, and it gave lower serum T_3 values. Serum T_4 was measured by a competitive protein binding technique (11). Normal values for these assays in this laboratory are TSH, 2–8 μU/ml; T_3, 70–150 ng/100 ml; and T_4, 5–11 μg/100 ml. All samples for the determination of either TSH, T_3, or T_4 from any one subject were analyzed in the same assay run. Statistical significance was determined by the paired t test (12).

RESULTS

Normal subjects—TSH response. Fig. 1 illustrates the mean serum TSH responses to i.v. TRH in normal subjects before and after chronic treatment with $T_3 + T_4$. Table II details the individual baseline TSH levels and maximum incremental TSH increase above the baseline levels (maximum ΔTSH) in the same subjects. The mean baseline level and the mean maximum ΔTSH in these young males were similar to those levels previously described for young (20–39-yr old) males with regard to both the 400 and 25 μg doses of TRH (8). Chronic treatment with 15 + 60 resulted in a 76% reduction of the maximum ΔTSH response to 400 μg TRH and an 87% reduction of the maximum ΔTSH response to 25 μg TRH (Table II). These reductions were statistically significant: $P < 0.01$ for the 400 μg TRH test, $P < 0.05$ for the 25 μg TRH test. Six of the eight subjects, moreover, had maximum ΔTSH responses (Table II) to 400 μg TRH that were below the normal range for 20–39-yr old males (8).

Chronic treatment of these normal subjects with 30 + 120 virtually abolished the mean serum TSH response to 400 μg TRH (Fig. 1), principally by suppressing the responses of the two subjects, J. M. and D. O., whose TSH responses had not been suppressed as much by the 15 + 60 treatment as had those of the other six subjects (Table II).

Normal subjects—T_3 and T_4 levels. The serum T_3 and

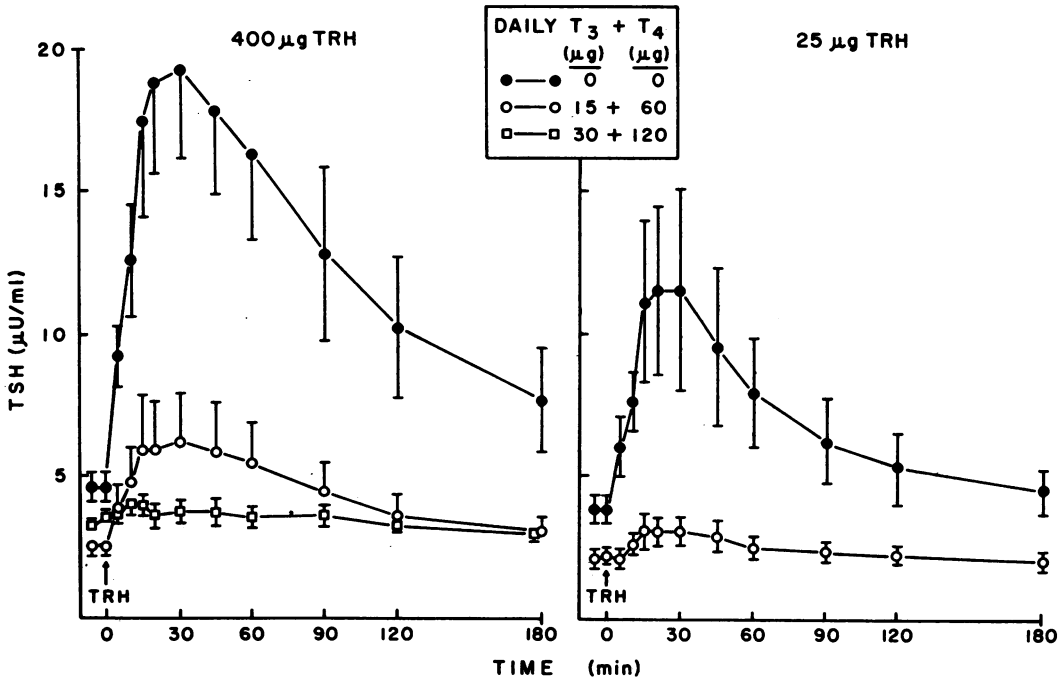

FIGURE 1 Effect of $T_3 + T_4$ treatment, 3–4 wk of each dosage, on the serum TSH response to the acute intravenous injection of TRH in normal young males. Eight subjects received 400 μg TRH, six received 25 μg. Values are expressed as means ±SEM.

T_4 levels in each subject on the morning of each 400 μg TRH test are shown in Table III. The 15 + 60 dosage produced no change in either the serum T_3 or T_4 levels under these circumstances. The 30 + 120 dosage produced a small increase of borderline statistical significance ($P < 0.05$) in the serum T_3 levels, but no significant change in the serum T_4 levels.

Normal subjects—T_3 and T_4 levels during a 24 hr period. To determine if the serum concentrations of T_3 and T_4 just before the TRH test, i.e. 24 hr after the last daily dose of $T_3 + T_4$, reflected accurately the serum levels at all times during the previous 24 hr, six additional normal subjects, aged 20–39, also were given $T_3 + T_4$. Serum T_3 and T_4 levels were determined at frequent intervals during 24-hr periods before beginning medication, at the end of 3–4 wk of taking 15 + 60 once each day, and at the end of 3–4 wk of taking 30 + 120 once each day (Fig. 2). No significant diurnal variation in either serum T_3 or T_4 levels was found before treatment. At the end of 3–4 wk of taking 15 + 60 each day, the mean serum T_3 level in the six subjects immediately before taking the last dose of 15 + 60 (zero time) was 103±8 ng/100 ml, not significantly different from that before treatment. The administration of the last dose of 15 + 60 produced a detectable rise in the serum T_3 level. The peak rise, to 163±10 ng/100 ml, occurred 2 hr after the ingestion of the dose and was significantly ($P < 0.01$) greater than the zero time that day. Serum T_4 levels were not affected, either at zero time or after ingestion of the last dose of 15 + 60.

At the end of 3–4 wk of taking 30 + 120 each day, the mean serum T_3 level at zero time was 148±8 ng/100 ml, significantly greater ($P < 0.01$) than before treatment. The administration of the last dose of 30 + 120 produced an even greater rise in the serum T_3 levels. The peak rise, to 308±18 ng/100 ml, again occurred 2 hr after the ingestion of the dose and was also significantly ($P < 0.001$) greater than the zero time that day. At this dosage of $T_3 + T_4$ the serum T_4 level at zero time was 7.6±0.3 μg/100 ml, not significantly greater than the pretreatment level, 6.9 μg/100 ml. The administration of the last dose of 30 + 120 produced a rise in serum T_4 level, which reached a plateau at 8.1 to 8.3 μg/100 ml between 2 and 8 hr after ingestion of the dose and, compared with the zero time that day, was of greater statistical significance ($P < 0.01$) at 6 and 8 hr. Even the peak serum T_4 levels, however, were well within the normal range.

Because the serum T_3 levels fluctuated significantly in the 24 hr after the ingestion of a dose of $T_3 + T_4$, the average T_3 level during the 24 hr was calculated for each subject. The calculation was made using the area under each subject's 24-hr T_3 response curve, as determined by planimetry. Fig. 3 shows the mean of the av-

TABLE II

Serum TSH Response to i.v. TRH in Normal Subjects Treated Chronically with $T_3 + T_4$*

	400 μg TRH						25 μg TRH			
T_3 (μg) + T_4 (μg)/day	0 0		15 60		30 120		0 0		15 60	
Subject	Basal TSH	Max‡ ΔTSH	Basal TSH	Max ΔTSH	Basal TSH	Max ΔTSH	Basal TSH	Max ΔTSH	Basal TSH	Max ΔTSH
	μU/ml		*μU/ml*		*μU/ml*		*μU/ml*		*μU/ml*	
N. B.	2.9	17.1	1.8	1.8	4.0	1.6	3.8	8.6	1.8	1.5
J. B.	3.5	9.7	1.5	1.2	3.3	2.4	3.2	4.8	1.5	0.0
T. D.	6.5	30.5	3.6	3.2	3.1	0.5	6.8	28.2	3.3	0.9
J. D.	4.8	12.7	2.1	0.0	3.1	0.5	2.7	2.1	2.1	0.6
B. F.	3.4	8.1	2.7	2.2	3.2	0.2	1.9	2.0	2.3	0.7
J. M.	4.6	12.2	4.2	9.3	4.2	0.2	—	—	—	—
D. O.	5.9	22.1	2.1	11.4	3.8	0.3	3.6	10.9	1.7	3.7
J. R.	5.4	9.1	2.1	0.5	2.0	0.6	—	—	—	—
Mean	4.6	15.2	2.5	3.7	3.3	0.8	3.7	9.4	2.1	1.2
±SEM	0.5	2.7	0.3	1.5	0.2	0.3	0.7	4.0	0.3	0.5

* For 3–4 wk at each $T_3 + T_4$ dosage before TRH administered.

‡ Maximum incremental increase in TSH above basal TSH.

eraged serum T_3 levels in the six subjects. The mean averaged pretreatment level, 98±7 ng/100 ml, is well within the normal range. The mean averaged serum T_3 level in these six subjects while they were taking 15 + 60 was 129±10 ng/100 ml, which is also well within the normal range, although significantly ($P < 0.01$) higher than the pretreatment level. The mean averaged serum T_3 level in these six subjects while they were taking 30 + 120 was 181±7 ng/ml, which is not only significantly higher ($P < 0.001$) than the pretreatment level in the same subjects, but is also above the normal range.

The means of the averaged 24-hr serum T_4 levels were 6.5±0.5 μg/100 ml before treatment, 6.5±0.4 μg/100 ml during 15 + 60 treatment, and 7.9±0.3 μg/100 ml during 30 + 120 treatment. The change from pretreatment to the higher dosage was of borderline significance ($P = 0.05$).

TABLE III

Serum T_3 and T_4 Concentrations in Normal Subjects Treated Chronically with $T_3 + T_4$*

		Serum T_3			Serum T_4		
Subject	T_3 (μg) + T_4 (μg)/day	0 0	15 60	30 120	0 0	15 60	30 120
		ng/100 ml			*μg/100 ml*		
N. B.		105	89	108	7.4	7.7	8.3
J. B.		104	110	129	6.5	6.9	6.2
T. D.		128	103	193	6.5	5.2	9.4
J. D.		109	156	138	7.0	8.7	8.9
B. F.		142	114	165	9.2	8.0	9.7
J. M.		165	110	141	7.1	8.3	6.3
D. O.		122	113	137	6.0	6.1	6.4
J. R.		80	88	113	5.7	5.4	6.9
Mean		119	110	141	6.9	7.0	7.8
±SEM		9	7	10	0.4	0.5	0.5

* For 3–4 wk at each $T_3 + T_4$ dosage before serum T_3 and T_4 measured.

Hypothyroid patients—TSH response. The hypothyroid patients received the same two doses of $T_3 + T_4$ as did the normal subjects and also received an intermediate dose, 22.5 + 90. TRH tests were done, as in the case of the normal subjects, before treatment and at the end of 3–4 wk of treatment with each dosage. Baseline and maximum ΔTSH levels after TRH in each subject at each $T_3 + T_4$ dosage level tested are listed in Table IV. Before treatment every patient had an elevated baseline TSH and a further increase in response to TRH. No correlation was noted between the magnitude of the baseline TSH and the magnitude of the max ΔTSH. During treatment with 30 + 120 every patient had a baseline TSH that was in the lower half of the normal range for this laboratory and a barely detectable response to TRH. The responses to TRH during treatment with the lower $T_3 + T_4$ dosages were variable and are better illustrated by Fig. 4. This figure shows the responses of the six subjects who received all three $T_3 + T_4$ dosages. The hatched area accompanying each patient's responses represents the normal range of TSH response for a person of that age and sex (8, 13). What was variable about the responses during treatment with the two smaller $T_3 + T_4$ dosages is that during treatment with 15 + 60 four patients had responses greater than the normal range ("hypothyroid") and two had responses within the normal range ("euthyroid"), while during treatment with 22.5 + 90 three patients had responses greater than

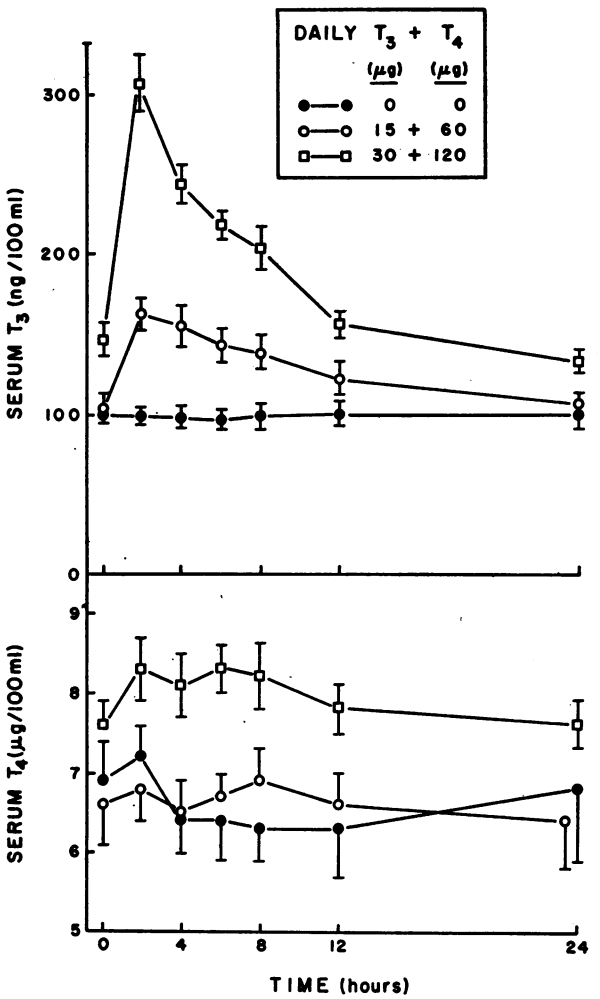

FIGURE 2 Effect of a single oral dose of $T_3 + T_4$ on the serum T_3 and T_4 levels in six normal subjects who had been taking that same dosage of $T_3 + T_4$ once daily for the previous 3–4 wk. Serum was obtained from each subject during a 24 hr period before any treatment, on the last day of 3–4 wk of 15 + 60 treatment, and on the last day of 3–4 wk of 30 + 120 treatment. Values expressed as mean ±SEM.

normal and three less than normal ("hyperthyroid"). What was quite consistent about the responses in all six patients was that for each patient there was one 7.5 + 30 increase in dosage which abruptly converted a maximum ΔTSH that was greater than, or at the upper limit of, normal to one that was subnormal. This abrupt change occurred when the dosage was increased from 15 + 60 to 22.5 + 90 in patients M. B., M. C., and E. R. and when the dosage increased from 22.5 + 90 to 30 + 120 in patients P. D., A. F., and M. Y.

Hypothyroid patients—T_3 and T_4 levels. The serum T_3 and T_4 levels in these hypothyroid patients during treatment with the three dosages of $T_3 + T_4$ are shown in Table V. Both the mean serum T_3 and T_4 levels increased progressively with each increase in dosage. The mean serum T_3 level at even the highest $T_3 + T_4$ dosage, however, was only in the upper part of the normal range. The mean serum T_4 levels at the highest $T_3 + T_4$ dosage were well within the normal range.

The changes in serum T_3 and T_4 levels associated with the abrupt changes in TSH response noted above are marked by arows in Table V. The mean serum T_3 level in the six patients at the time of the supranormal response was 105±5 ng/100 ml and at the time of the subnormal response was 129±9 ng/100 ml. The corresponding serum T_4 levels were 4.9±0.8 and 6.3±0.5 μg/100 ml.

DISCUSSION

The data presented here demonstrate that the chronic administration of small quantities of exogenous $T_3 + T_4$ to normal subjects and to patients with partially treated, primary hypothyroidism results in marked inhibition of

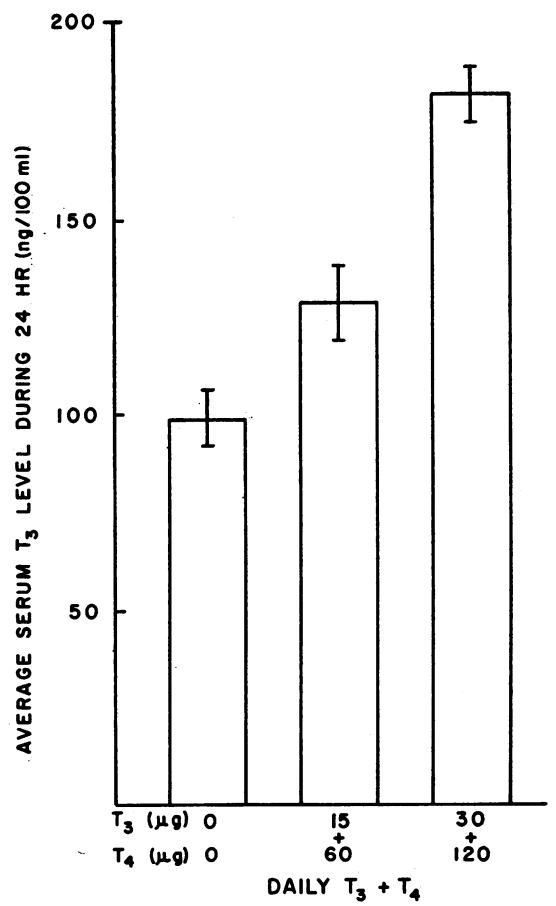

FIGURE 3 The average serum T_3 levels during 24 hr in six normal subjects taking $T_3 + T_4$ for 3–4 wk, as calculated by planimetry from the T_3 curves in Fig. 2. Values are expressed as means ±SEM.

TABLE IV

Serum TSH Response to i.v. TRH, 400 μg, in Patients with Primary Hypothyroidism Treated Chronically with $T_3 + T_4$*

Patient	T_3 (μg) + T_4 (μg)/day	0 + 0		15 + 60		22.5 + 90		30 + 120	
		Basal TSH	Max ΔTSH‡	Basal TSH	Max ΔTSH	Basal TSH	Max ΔTSH	Basal TSH	Max ΔTSH
		μU/ml		μU/ml		μU/ml		μU/ml	
M. B.		126.5	63.5	26.8	73.2	2.6	3.5	3.7	2.0
M. C.		54.3	127.8	9.5	12.5	4.1	2.7	3.2	0.7
P. D.		40.8	77.2	17.5	44.5	11.3	26.7	4.7	1.8
A. F.		54.4	63.1	12.2	37.8	8.9	34.1	4.1	2.0
E. G.		28.5	16.5	—	—	2.6	0.3	3.5	0.5
D. G.		31.5	88.5	—	—	—	—	2.0	0.1
L. H.		56.5	123.1	—	—	—	—	3.1	1.7
R. N.		300.0	90.0	—	—	—	—	3.1	0.9
E. R.		72.3	307.7	5.8	28.2	2.5	0.2	1.5	0.3
R. S.		207.5	122.5	—	—	5.9	50.1	3.1	0.1
M. Y.		64.7	123.5	11.1	88.9	5.8	23.2	4.3	0.6
Mean		94.3	109.4	13.8	47.5	5.5	17.6	3.3	1.0
±SEM		25.8	22.3	3.0	11.7	1.1	6.6	0.3	0.2

* For 3–4 wk at each $T_3 + T_4$ dosage before TRH administered.

‡ Maximum incremental increase in TSH above basal TSH.

TRH-induced TSH release. Marked inhibition occurs even when the serum T_3 and T_4 levels are not increased above the normal range. One striking example of this inhibition is the ability of 15 + 60, when administered to normal subjects for 3–4 wk, to cause a 76% reduction in the TSH response to 400 μg TRH and an 87% reduction in the response to 25 μg TRH. This degree of inhibition is especially significant considering that (*a*) this

TABLE V

Serum T_3 and T_4 Concentrations in Patients with Primary Hypothyroidism Treated Chronically with $T_3 + T_4$*

Patient	T_3 (μg) + T_4 (μg)/day	Serum T_3 0 + 0	15 + 60	22.5 + 90	30 + 120	Serum T_4 0 + 0	15 + 60	22.5 + 90	30 + 120
		ng/100 ml				μg/100 ml			
M. B.		40	93 →‡	123	116	2.3	4.1 →	4.7	6.4
M. C.		40	93 →	129	97	1.4	4.5 →	5.9	6.0
P. D.		108	113	104 →	119	4.8	5.5	4.7 →	6.3
A. F.		30	75	98 →	106	1.3	2.7	3.9 →	5.3
E. G.		40	—	88	127	2.0	—	5.3	6.4
D. G.		87	—	—	170	4.1	—	—	7.9
L. H.		47	—	—	85	4.0	—	—	8.3
R. N.		35	—	—	159	1.4	—	—	5.9
E. R.		69	119 →	127	145	4.6	5.5 →	7.1	7.9
R. S.		67	—	159	204	2.0	—	5.8	9.7
M. Y.		97	136	120 →	172	4.6	5.4	6.6 →	8.1
Mean		60	105	119	136	3.0	4.6	5.5	7.1
±SEM		8	8	8	11	0.5	0.5	0.4	0.4

* For 3–4 wk at each $T_3 + T_4$ dosage before serum T_3 and T_4 measured.

‡ The arrows indicate the changes in T_3 and T_4 levels associated with the abrupt changes in TSH response from greater than, or at the upper limit of, normal to subnormal illustrated in Fig. 4.

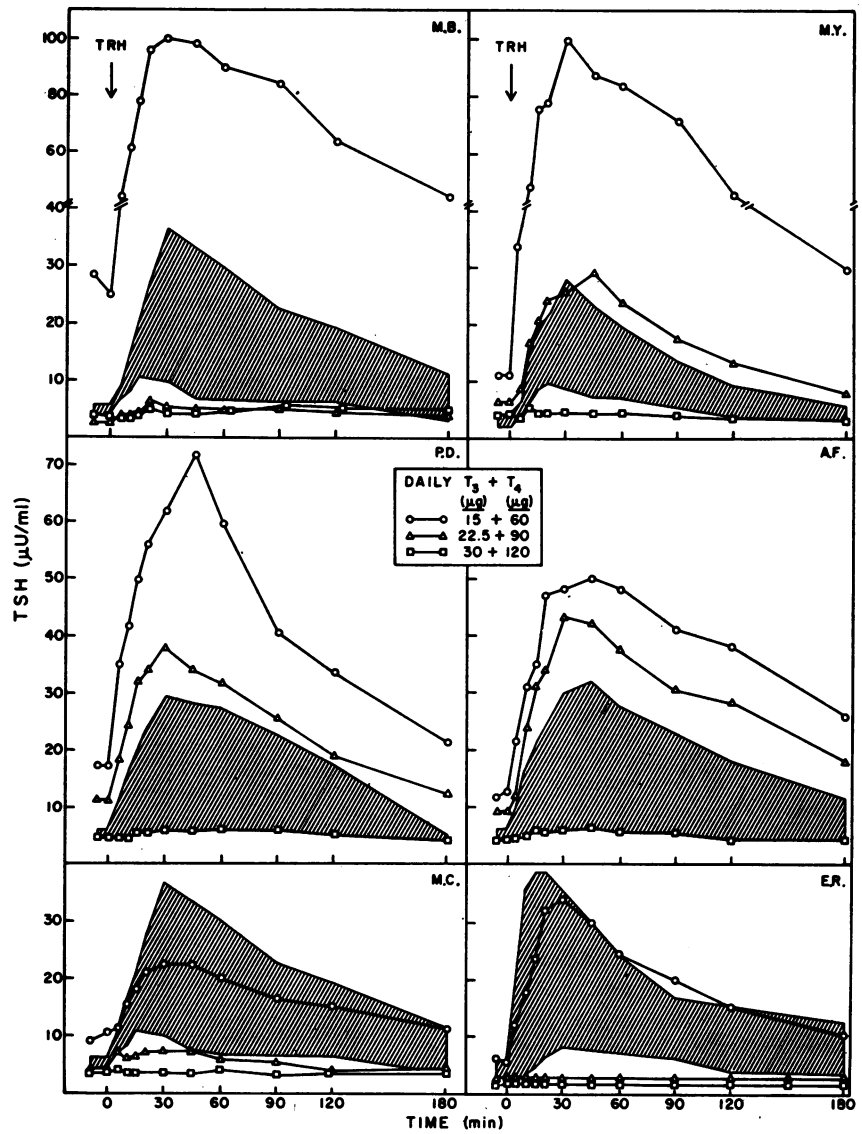

FIGURE 4 Effect of three dosages of $T_3 + T_4$ on the serum TSH response to the acute i.v. injection of TRH in six patients with primary hypothyroidism. Not shown here are the pretreatment TSH levels, which were higher than those at the lowest treatment dosage. The hatched area in each panel represents the normal range of response for a person of that patient's age and sex (8, 13). For each patient there was one increase in dosage of 7.5 μg T_3 + 30 μg T_4 that abruptly converted a response that was greater than, or at the upper limit of, normal to one that was subnormal.

dosage of $T_3 + T_4$ is less than a replacement dosage, as documented by its failure in the primary hypothyroid patients to lower baseline TSH levels to normal (Table IV); and that (*b*) this dosage of $T_3 + T_4$ causes only a small rise in the serum T_3 level, not above the normal range, and no measurable change in the serum T_4 levels (Figs. 2 and 3). Another striking example of this inhibition is the ability of an increase of only 7.5 + 30 in the dosage administered to patients with partially-treated primary hypothyroidism to reduce the serum TSH response to TRH from above normal or in the upper normal range to below normal (Fig. 4). Although in three of the patients this obliteration of the response occurred when the dose was raised from 15 + 60 to 22.5 + 90 and in the other three patients the obliteration occurred when the dose was raised from 22.5 + 90 to 30 + 120, the abrupt change from a supranormal or high-normal response to a subnormal response

occurred uniformly with an increase in dosage of only 7.5 + 30. The mean increases in serum T_3 and T_4 levels associated with these six abrupt changes in TSH response, moreover, were only 25 ng/100 ml and 1.3 μg/100 ml.

No studies have been previously reported on the effect of dosages of $T_3 + T_4$ as small as those employed here on TRH-induced TSH release. In one related study (14) a single dose of 100 μg T_3 was given 6 or 18 hr before the TRH test. Although six of the eight subjects had a TSH response, the responses are difficult to interpret, because no control TRH tests were done before the administration of the T_3. TSH response to TRH has been tested also in overt hyperthyroidism and found to be markedly subnormal (6, 7). The serum protein-bound iodine (PBI) levels in 19 of the 20 hyperthyroid patients in whom these levels were reported, however, were elevated (7). These elevations contrast to the normal serum T_4 levels in the subjects treated with $T_3 + T_4$ reported here.

One implication of the data presented here is that the ranges of serum T_3 and T_4 concentrations in which TSH response to TRH is normal must be very small. Therefore, a replacement dosage of thyroid hormone, one sufficient to maintain a hypothyroid patient in a euthyroid state with a serum TSH level that is not elevated, is generally also a suppressive dosage, capable of suppressing TSH secretion below normal.

Another implication of the data presented here is that the administration of usually effective doses of TRH would not be effective in a patient with an autonomously functioning thyroid gland producing serum T_3 and T_4 levels higher than his antecedent normal gland did, but not necessarily higher than the normal ranges of serum T_3 and T_4. This postulated phenomenon may explain why those patients reported by Ormston, Garry, Cryer, and Besser (7) with suspected hyperthyroidism and serum PBI levels in the upper part of the normal range, as well as those with PBI levels above normal, did not have serum TSH responses to TRH.

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