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The relative roles of triiodothyronine (T_3) and thyroxine (T_4) in modulating pituitary responsiveness to thyrotropin-releasing hormone (TRH) have been assessed. (a) 10 hyperthyroid patients with elevated serum T_2 and T_4 levels showed no pituitary response to TRH. After 2 wk of propylthiouracil therapy T_4 levels had fallen to normal in only five patients while T_2 levels were normal in all. Pituitary responsiveness to TRH returned in all patients with normal or high T_4 concentrations. (b) Patients with isolated elevations of serum T_3 (T_3 toxicosis) failed to respond to TRH. TRH responsiveness was restored when T_3 levels fell to normal after propylthiouracil therapy. (c) When pituitary responsiveness to TRH was tested 60 min after a single oral dose of 50 μ g of T_3 , which increased serum T_3 levels to slightly above the normal range, no rise in thyrotropin (TSH) was seen in six subjects. These findings indicate that T_3 elevations alone can rapidly inhibit pituitary responsiveness to TRH.

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Modulation of Pituitary Responsiveness to Thyrotropin-Releasing Hormone by Triiodothyronine

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ABSTRACT The relative roles of triiodothyronine (T_3) and thyroxine (T_4) in modulating pituitary responsiveness to thyrotropin-releasing hormone (TRH) have been assessed. (a) 10 hyperthyroid patients with elevated serum T_3 and T_4 levels showed no pituitary response to TRH. After 2 wk of propylthiouracil therapy T_4 levels had fallen to normal in only five patients while T_3 levels were normal in all. Pituitary responsiveness to TRH returned in all patients with normal or high T_4 concentrations. (b) Patients with isolated elevations of serum T_3 (T_3 toxicosis) failed to respond to TRH. TRH responsiveness was restored when T_3 levels fell to normal after propylthiouracil therapy. (c) When pituitary responsiveness to TRH was tested 60 min after a single oral dose of 50 μ g of T_3 , which increased serum T_3 levels to slightly above the normal range, no rise in thyrotropin (TSH) was seen in six subjects. These findings indicate that T_3 elevations alone can rapidly inhibit pituitary responsiveness to TRH.

INTRODUCTION

Intravenous administration of thyrotropin-releasing hormone (TRH)¹ to laboratory animals and to man results in a prompt rise in plasma levels of thyrotropin

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¹Abbreviations used in this paper: T_3 , triiodothyronine; T_4 , thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyrotropin.

(TSH) (1-3). It has been shown that the pituitary response to TRH is modulated by the level of circulating thyroid hormone (4-6). However, it is unclear whether thyroxine (T_4) alone or triiodothyronine (T_3) alone are capable of inhibiting the pituitary response to TRH or whether a combination of both hormones is required. The advent of a reliable and accurate radioimmunoassay for T_3 (7) has now allowed us to investigate the relative roles of T_3 and T_4 in modulating the pituitary response to TRH. We have therefore studied the response to TRH in several clinical settings in which either T_3 , T_4 or both were elevated.

METHODS

Three groups of patients were studied.

Group 1. 10 patients with diffuse toxic goiter (Graves' disease), 22-46 yr of age, were studied. The patients, six women and four men, all had diffuse enlargement of the thyroid; seven had either mild or moderate ophthalmopathy. Pretreatment levels of T_4 and T_3 were elevated in all 10 patients (see Table I). TRH administration was performed before the initiation of antithyroid therapy, and 2 wk later while on a course of propylthiouracil, 400-800 mg/day.

Group 2. Six patients with T_3 toxicosis, two men and four women, ranging in age from 28 to 43 yr, were studied. Like the other patients we have previously described with this syndrome, they had typical clinical features of hyperthyroidism associated with elevated serum concentrations of T_3 and normal serum T_4 levels (8). Five had diffuse toxic goiter; one had an autonomous thyroid adenoma. All six patients had elevated T_3 values and normal or elevated thyroidal uptakes of radioiodine which were nonsuppressible with exogenous T_3 . Total and free T_4 levels were normal in all. TRH administration was performed before the institu-

TABLE I
Serum Thyroid Hormone Levels in Conventional Hyperthyroidism and in
T₃ Toxicosis before and after Drug Therapy

Subject	Age	Sex	Before therapy		Therapy with propylthiouracil	After therapy	
			T ₃	T ₄ *		T ₃	T ₄
			ng/100 ml†	μg/100 ml		mg/day	ng/100 ml
Conventional hyperthyroidism (group 1)							
1	39	F	336	15	400	140	16.0
2	32	M	360	13	400	128	8.1
3	22	F	570	19.5	600	148	13.2
4	40	M	364	13	400	112	4.3
5	44	F	410	20	800	140	10.5
6	46	F	400	13	600	138	13.0
7	29	M	1200	20	800	150	15.1
8	27	F	420	14	400	120	7.5
9	35	F	600	16.5	600	152	9.0
10	28	M	460	17	600	150	14.4
T ₃ toxicosis (group 2)							
1	43	F	400	8.5	600	140	8.0
2	28	F	240	8.0	800	128	8.0
3	34	F	210	7.6	400	114	7.4
4	32	M	420	8.1	600	126	7.0
5	32	M	340	9.0	600	140	6.5
6	38	F	400	10.0	600	138	7.3

* Normal range 4–11 μg/100 ml, expressed as total hormone.

† Normal range 96–172 ng/100 ml, expressed as total hormone.

tion of antithyroid therapy, and again 2 wk after the administration of propylthiouracil, 400–800 mg/day.

Group 3. Seven normal volunteers were tested before, and 60 min after, an oral dose of 50 μg of T₃, as Cytomel (Smith, Kline, and French Laboratories, Philadelphia, Pa.) (Table II). The subjects had no history of thyroid disease, were clinically euthyroid, and had normal T₃ and T₄ values. The initial TRH administration in these subjects was performed 3 days later, 60 min after ingestion of 50 μg T₃.

TRH administration was performed in all patients in the morning after an overnight fast. An intravenous cannula was inserted in an antecubital vein for administration of TRH and withdrawal of blood samples. Basal blood samples were obtained and 400 μg TRH (Abbott Laboratories, North Chicago, Ill.) was administered over a 30 s interval. Blood samples were obtained in heparinized syringes at 10, 20, 30, 40, 60, 90, 120, and 180 min, centrifuged, and the plasma frozen until assayed. T₃ (7) and TSH (9) were measured by radioimmunoassay; T₄ was determined by competitive protein-binding analysis (Boston Medical Lab., Boston, Mass.).

RESULTS

Group 1. Pretreatment levels of T₃ and T₄ in the 10 patients with conventional hyperthyroidism are listed in Table I. T₄ levels were all above normal and ranged from 13 to 20 μg/100 ml; T₃ concentrations were likewise elevated and ranged from 336 to 1200 ng/100 ml. Basal levels of TSH were undetectable in all subjects, and after administration of TRH no TSH rise was

noted. After 2 wk of propylthiouracil administration, T₃ levels had fallen to normal in all patients, ranging from 126 to 150 ng/100 ml. T₄ concentrations also fell, but not as dramatically as T₃. In five subjects, T₄ levels were still above the normal range (see Table I).

On retesting with TRH, both the patients with normal T₃ and T₄ levels, as well as those with normal T₃ and high T₄ concentrations, showed a prompt rise in TSH levels. Indeed, the responses in both groups were virtually identical, reaching a peak of 9.9±1.1 μU/ml (mean ±SEM) in patients with a high T₄ level and 10.1±1.3 μU/ml in patients with a normal T₄ concentration. (See Fig. 1.)

Group 2. The six patients with T₃ toxicosis all had elevated T₃ concentrations, ranging from 210 to 420 ng/100 ml. T₄ values in all were normal. Basal TSH levels were not detectable and did not rise after TRH administration (see Fig. 2). After 2 wk of propylthiouracil administration, T₃ levels fell to normal in all six subjects. T₄ levels also fell slightly, but remained within the normal range. Readministration of TRH at this time demonstrated a return of pituitary responsiveness, peak TSH levels ranging from 4.7 to 11 μU/ml.

Group 3. Before administration of Cytomel, all seven subjects demonstrated a normal response to TRH (Table II). 3 days after the initial TRH test, 50 μg of

TABLE II
Effect of Oral Administration of Triiodothyronine (T_3) on Serum T_3 Levels and Responsiveness to TRH (group 3)

Subject	Age	Sex	Basal		Plasma T_3 , ng/100 ml after 50 μ g T_3 by mouth			Peak plasma TSH, μ U/ml after 400 μ g TRH i.v.	
			T_4	T_3	60 min	120 min	180 min	Basal study	Study 60 min after 50 μ g T_3 by mouth
			μ g/100 ml	ng/100 ml					
1	21	M	5.8	100	210	240	290	12.8	Nondetectable
2	23	M	6.0	112	190	218	196	13.6	Nondetectable
3	30	M	7.2	114	188	216	320	11.4	Nondetectable
4	38	M	7.9	100	910	240	230	8.8	Nondetectable
5	41	F	6.4	130	220	340	271	12.4	Nondetectable
6	43	F	6.3	118	183	212	270	11.3	Nondetectable
7	31	F	5.9	104	235	400	350	13.4	Nondetectable

T_3 was administered orally to all subjects. 60 min later T_3 levels ranged from 183 to 235 ng/100 ml (Table II). Readministration of TRH at this time failed to produce a rise in TSH. T_3 levels continued to rise reaching peak values at 2–3 h.

DISCUSSION

Pituitary responsiveness to TRH clearly is affected by the level of circulating thyroid hormone. In vitro studies with pituitary cell cultures have demonstrated that preincubation with either T_4 or T_3 prevents the TRH-mediated release of TSH (4, 5). Animal studies have shown that implantation of T_4 into the pituitaries (10) or hy-

pothalamus (11) of rats prevents the expected rise in TSH after TRH administration. Studies in man have also shown that thyroid hormone levels play a role in regulating TRH response. Patients with primary hypothyroidism who have low circulating levels of thyroid hormone are very responsive to TRH (12), while hyperthyroid subjects are unresponsive (13). Furthermore, if T_4 alone is given to a patient with primary hypothyroidism, progressive blunting of pituitary responsiveness to TRH can be demonstrated as the dose of T_4 is gradually increased (14).

However, the results of such observations are difficult to interpret since it is impossible to differentiate the effects of T_4 alone from that of T_3 arising from conversion of T_4 . That this conversion of T_4 to T_3 can be quantitatively significant has been documented by a number of recent studies (15–18) as has the observa-

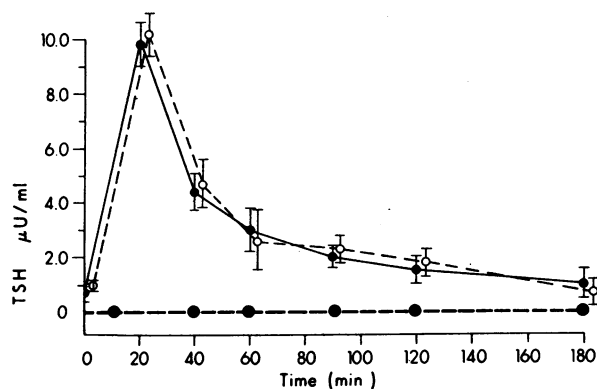


FIGURE 1 Pituitary responsiveness to TRH in Grave's disease. Before treatment (closed circles, heavy-dashed line) no TSH response was detected in any of the 10 patients after intravenous administration of 400 μ g of TRH at 0 time. After therapy with propylthiouracil both the five patients with a high serum T_4 level (closed circles, solid line) and the five with normal serum T_4 concentrations (open circles, dashed line) showed a prompt rise in serum TSH levels. Each point represents the mean of five subjects plus or minus the standard error of the mean.

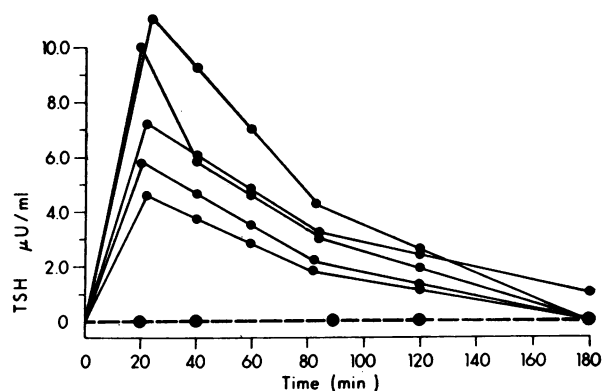


FIGURE 2 Pituitary responsiveness to TRH in T_3 toxicosis. Before therapy with propylthiouracil none of the six patients showed a TSH response to the intravenous administration of 400 μ g of TRH at 0 time (closed circles, dashed line). After treatment a TSH rise was seen in all subjects (closed circles, solid line).

tion that pituitary tissue is capable of converting T_4 to T_3 (19).

In view of recent evidence suggesting that T_3 contributes a major portion of the calorogenic potency of thyroid hormones (20–22), and indeed may be the active form, we have sought to delineate the relative roles of T_3 and T_4 in modulating pituitary responsiveness to TRH by administering TRH to patients in whom one or the other hormone is elevated.

Patients with untreated hyperthyroidism have high serum concentrations of both T_4 and T_3 . However, after the initiation of antithyroid drug therapy, T_3 , because of its more rapid turnover, may fall to normal while serum T_4 concentrations remain elevated. After 2 wk of propylthiouracil therapy, of the 10 hyperthyroid patients in group 1, T_4 had returned to normal in only five; T_3 was normal in all. Of considerable interest was the fact that administration of TRH to these subjects produced a normal response whether T_4 was elevated or normal. Thus, in these patients, a high T_4 level alone, associated with normal T_3 concentration, did not suppress pituitary responsiveness to 400 μg of TRH. However, the possibility that a lower dose of TRH might have unmasked a blunted TSH response has not been excluded. Propylthiouracil has been shown to block conversion of T_4 to T_3 (23). The potential relevance of this observation to our findings is currently being assessed in our laboratory by administering TRH to hyperthyroid patients receiving methimazole or iodides.

In order to assess whether T_3 alone is capable of blunting TRH responsiveness, we administered TRH to patients with T_3 toxicosis who had isolated elevations of T_3 and normal free and total T_4 levels. The absence of a TSH response would clearly indicate that, in this circumstance, elevated serum levels of T_3 alone are capable of modulating the pituitary response to TRH. When T_3 levels were lowered by propylthiouracil administration, responsiveness to TRH quickly returned.

These findings are consistent with those of Snyder and Utiger (24) who showed that the TRH-induced TSH release in eight normal subjects was extremely sensitive to the chronic administration of increasing quantities of a mixture of T_3 and T_4 which did not raise serum T_3 and T_4 levels above the normal range. 3 wk after administration of a mixture of 15 μg T_3 and 60 μg T_4 mean serum T_3 levels in these subjects rose from 98 $\mu\text{g}/100$ ml to 129 $\mu\text{g}/100$ ml; serum T_4 levels did not rise from a value of 6.5 $\mu\text{g}/100$ ml. At this time TRH responsiveness was strikingly inhibited as assessed with 400 μg and 25 μg of TRH. These findings indicate that even a small increment in T_3 concentration within the normal range, unaccompanied by a rise in serum T_4 , is capable of inhibiting pituitary responsiveness to TRH.

Our studies on the subjects in group 3 demonstrate that pituitary responsiveness can be rapidly inhibited. When TRH responsiveness was tested 60 min after a single oral dose of 50 μg of T_3 which increased serum T_3 levels to slightly above the normal range, no rise in TSH was seen. These data correlate with recent findings by Schadow, Schwartz, Surles, and Oppenheimer (25) which suggest that the pituitary contains a highly specific set of saturable binding sites for T_3 but not for T_4 and are consistent with their postulate that specific pituitary T_3 binding sites may well mediate the thyroid pituitary negative feedback system. In view of the rapid metabolic clearance of T_3 compared to T_4 , modulation of pituitary response by T_3 rather than T_4 would provide finer control of the body's changing needs for TSH.

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