Hyperresponse to Thyrotropin-Releasing Hormone Accompanying Small Decreases in Serum Thyroid Hormone Concentrations

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ABSTRACT To determine whether pituitary thyrotropin (TSH) responsiveness to thyrotropin-releasing hormone (TRH) is enhanced by small decreases in serum thyroxine (T_4) and triiodothyronine (T_3), 12 euthyroid volunteers were given 190 mg iodide po daily for 10 days to inhibit T_4 and T_3 release from the thyroid. Basal serum T_4, T_3, and TSH concentrations and the serum T_4 and TSH responses to 400 μg TRH i.v. were assessed before and at the end of iodide administration. Iodide induced small but highly significant decreases in basal serum T_4 (8.0±1.6 vs. 6.6±1.7 μg/100 ml; mean ± SD) and T_3 (128±15 vs. 110±22 ng/100 ml) and increases in basal serum TSH (1.3±0.9 vs. 2.1±1.0 μU/ml). During iodide administration, the TSH response to TRH was significantly increased at each of seven time points up to 120 min. The maximum increment in serum TSH after TRH increased from a control mean of 8.8± 4.1 to a mean of 13.0±2.8 μU/ml during iodide administration. As evidence of the inhibitory effect of iodide on hormonal release, the increment in serum T_3 at 120 min after TRH was significantly lessened during iodide administration (61±42 vs. 33±24 ng/100 ml). These findings demonstrate that small acute decreases in serum T_4 and T_3 concentrations, resulting in values well within the normal range, are associated both with slight increases in basal TSH concentrations and pronounced increases in the TSH response to TRH. These results demonstrate that a marked sensitivity of TSH secretion and responsiveness to TRH is applicable to decreasing, as well as increasing, concentrations of thyroid hormones.

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INTRODUCTION

The discovery, characterization, and chemical synthesis of the hypothalamic thyrotropin-releasing hormone (TRH)[1] has greatly spurred an understanding of the manner in which feedback regulation of thyroid function is effected in animals and man (1–4). It has become clear, for example, that regulation takes place predominately in the pituitary, where the stimulatory effect of TRH on the secretion of thyrotropin (TSH) is antagonized by the inhibitory effects of the thyroid hormones. Within this context, it is not unexpected that the response to exogenous TRH with respect to TSH secretion is greatly inhibited or abolished in patients with frank hyperthyroidism and enhanced in patients with primary myxedema (5–8). More surprising is the fact that in euthyroid individuals, small increases in the concentrations of thyroxine (T_4) and triiodothyronine (T_3) in serum, leaving them still well within the normal range, also inhibit the response to TRH (9, 10). Moreover, similar blunting or abolition of the response to TRH is seen in patients who are euthyroid by standard clinical and laboratory criteria, but who have an autonomous thyroid nodule suppressing function in the remainder of the gland (11). It would be unreasonable to

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

TABLE I

The Effect of Iodide Administration on Serum Concentrations of T_4, T_3, and TSH

Subject	Serum T_4		Serum T_3		Serum TSH	
	Control*	Iodide‡	Control	Iodide	Control	Iodide
	μg/100 ml		*ng/100 ml*		*μU/ml*	
1	10.2	7.9	140	114	3.0	3.8
2	10.2	9.1	135	129	3.1	2.9
3	11.5	9.2	124	90	<1.3	<1.3
4	8.0	8.1	95	70	<1.3	3.4
5	6.6	4.2	132	114	<1.3	2.7
6	7.4	7.2	139	117	<1.3	<1.3
7	7.7	5.4	136	146	<0.6	1.9
8	7.2	4.9	136	88	<0.6	2.1
9	8.2	6.6	135	115	0.9	1.7
10	6.2	4.7	110	99	<0.6	0.7
11	6.0	5.2	141	141	<0.6	1.2
12	8.7	7.3	108	100	1.9	1.9
Mean	8.0	6.6	128	110	1.3	2.1
SD	1.6	1.7	15	22	0.9	1.0
P Value (Paired *t* test)	<0.001		<0.005		<0.01	
Normal range§	4–11.5		80–185		<0.6, <1.3–5	

*Mean value of 3 successive days.

‡ Mean value of last 3 days of iodide administration (190 mg daily for 10 days).

§ As defined in this laboratory in normal euthyroid subjects.

postulate that such suppression reflects secretion by the nodule of precisely physiological quantities of hormone, rather than a slight excess. Thus, it is evident that the set point of feedback regulation is tuned to detect not only gross, but also subtle, increases in the availability of thyroid hormones.

It also seems clear that regulatory mechanisms within the pituitary are capable of detecting rather subtle deficiencies in the availability of thyroid hormones, but little is known of the rapidity of such response. One factor that has hampered studies of this topic is that a predictable means of producing acute small decreases in the supply of thyroid hormones in euthyroid individuals has not been apparent. Recently, however, we have demonstrated that pharmacological doses of iodide produce in normal individuals a slight decrease in serum T_4 and T_3 concentrations that is evident within a few days (12). In this report we describe the effects of such treatment on the intrapituitary regulatory response, as judged from the rise in serum TSH after synthetic TRH administration.

METHODS

Studies were performed in nine male and three female normal volunteers ranging in age between 23 and 35 yr. During a control period, blood was obtained daily from each subject between 9:00 and 11:00 a.m. for 3 consecutive days. On the 3rd day, samples of blood were obtained 10 min before and immediately before an i.v. pulse injection of 400 μg synthetic TRH, as well as 10, 20, 30, 45, 60, 90, and 120 min thereafter. Subjects were then given five drops of Lyne's saturated solution of potassium iodide twice daily (190 mg iodide daily) for 10 days. Blood was drawn in the morning on the last 3 days of iodide administration, and on the last (10th) day another TRH test was done, as described above. Sera were quickly obtained from the foregoing samples of blood and were stored frozen at −20°C until required for analyses.

Serum T_4 concentration was measured by the Tetralute method (Ames Co., Div. of Miles Lab, Inc., Elkhart, Ind.) (13), and serum T_3 concentration by radioimmunoassay using 8-anilino-1-naphthalene sulfonic acid to inhibit binding of T_3 to plasma proteins. Charcoal coated with bovine serum albumin was used to separate bound from free hormone (14). Serum TSH concentration was measured by a double antibody technique[3] (15).

For each of the hormones measured, all samples from a given subject were assayed concurrently and in duplicate. For each subject, base-line values during the control and iodide treatment periods, i.e. those obtained without exogenous TRH stimulation, were calculated as the mean of the three values obtained during the period. The experimental design permitted statistical analyses of the results obtained by the paired *t* test (16).

[3] The human TSH and TSH antiserum were kindly provided by the Pituitary Agency of the National Institutes of Health, Bethesda, Md.

TABLE II

*The Effect of Iodide Administration on the Serum TSH and T_3 Responses to TRH**

Subject	Maximum Δ TSH after TRH		Serum T_3 120 min after TRH		Δ T_3 after TRH‡	
	Control	Iodide§	Control	Iodide	Control	Iodide
	μU/ml		*ng/100 ml*		*ng/100 ml*	
1	15.7	17.4	190	120	53	28
2	14.0	14.0	235	155	95	28
3	9.6	9.6	150	95	28	11
4	5.3	10.0	135	100	35	30
5	4.3	11.5	190	175	72	60
6	7.0	9.7	155	125	43	20
7	3.7	9.6	265	200	125	53
8	8.0	16.0	165	120	23	20
9	11.7	12.7	155	95	15	−15
10	7.3	15.6	155	115	35	33
11	5.2	13.2	285	210	148	78
12	13.9	16.0	170	135	60	45
Mean	8.8	13.0	187	137	61	33
SD	4.1	2.8	48	39	42	24
P Value (Paired *t* test)	<0.005		<0.001		<0.005	

* 400 μg i.v.

‡ The difference in T_3 concentration between the basal and the 120 min post-TRH value.

§ TRH test performed on the 10th day of iodide administration (190 mg daily).

RESULTS

All values for base-line serum T_4, T_3, and TSH concentrations were normal during control periods, and although significantly altered during iodide administration, remained well within the normal range (Table I).

Base-line serum T_4 and T_3 concentrations. The serum T_4 concentration decreased during iodide administration in 11 of 12 subjects, the mean value changing from 8.0±1.6 (mean ± SD) to 6.6±1.7 μg/100 ml ($P < 0.001$). The serum T_3 concentration decreased in 10 subjects, remained unchanged in 1, and increased in another. In both of the latter subjects, a distinct decrease in the serum T_4 concentration occurred during iodide administration. For the group as a whole, the mean serum T_3 concentration decreased from 128±15 to 110±22 ng/100 ml ($P < 0.005$).

Base-line serum TSH concentration. During the control period, base-line values for the serum TSH concentration were below the limit of detectability of the particular assay (0.6 or 1.3 μU/ml) in 8 of the 12 subjects. To make possible calculation of a mean value for the entire group, values in these eight subjects were taken to be equal to the value of this lower limit. By this method, the mean base-line serum TSH during the control period was calculated to be 1.3±0.9 μU/ml. During iodide administration, the base-line serum TSH concentration increased in eight subjects, remained undetectable in 2, unchanged in 1, and decreased in another, the mean value calculated as described above, increasing significantly to 2.1±1.0 μU/ml ($P < 0.01$). However, even during iodide administration, none of the values for basal serum TSH concentration exceeded the upper limit of the normal range (5 μU/ml) as defined in this laboratory.

Serum TSH response to TRH (Table II). During the control period, the maximum increment in the serum TSH concentration after TRH administration averaged 8.8±4.1 μU/ml (range 3.7–15.7). During iodide administration, the maximum increment in the serum TSH was greater than during the control test in 10 of 12 subjects, and was unchanged in 2. For the group as a whole, the maximum increment averaged 13.0±2.8 (range, 9.6–17.4), a significant increase from the control value ($P < 0.005$). This increase in the TRH response was evident at each time period after TRH administration studied (Fig. 1).

Serum T_3 response to TRH (Table II). The maximum increase in the serum T_3 concentration that followed TRH administration was evident in the 120-min samples in all subjects during the control period and in

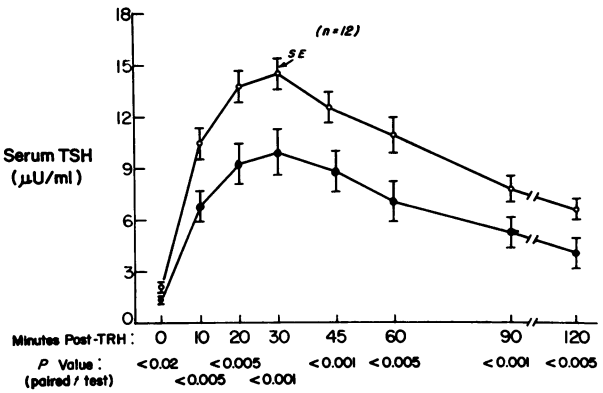

FIGURE 1 The effect of iodide administration (190 mg daily for 10 days) on the serum TSH response to 400 μg TRH i.v. (●), before iodide; (○), during iodide administration.

11 of 12 subjects during iodide administration. In these 120-min samples, the mean serum T_3 concentration during control tests (187±48 ng/100 ml) was significantly higher than during the TRH test performed while subjects were receiving iodide (137±39 ng/100 ml; $P < 0.001$). This change was a reflection of the fact that the increase in serum T_3 concentration produced by TRH was significantly less during iodide administration (33± 24 ng/100 ml) than during the control period (61±42 ng/100 ml; $P < 0.005$).

DISCUSSION

The nature of feedback regulation of TSH secretion at the level of the pituitary is such that frank hyperthyroidism inhibits, and hypothyroidism exaggerates, the secretory response to TRH. Until recently, however, there has been uncertainty as to the extent and duration of the altered availability of thyroid hormone that is required to influence responsiveness to TRH. Recent studies have demonstrated, however, that clinically undetectable increases in the availability of thyroid hormones soon blunt or abolish the rise of serum TSH that TRH normally induces (9–11). The present studies complement these observations in demonstrating that very slight, and relatively acute, decreases in serum T_4 and T_3 concentrations, which leave values for these functions and for serum TSH concentrations as well clearly within the normal range, are associated with distinct increases in the secretory response to TRH. It might be reasoned that the slight increase in basal serum TSH concentration and increased responsiveness to TRH that we have observed is due, not to the decrease in serum T_4 and T_3 concentrations that iodide induced, but rather to a direct effect of iodide on the pituitary, increasing its sensitivity to endogenous or exogenous TRH. Although not directly tested, this possibility is rendered quite unlikely by the observation that both serum and pituitary concentrations of thyroidectomized rats are unchanged by iodide administration (17). Hence, our observations, together with those of previous workers cited above, indicate how sensitively the feedback mechanism is tuned to detect and respond promptly to slight alterations in the supply of thyroid hormone, insufficient to alter detectably the peripheral metabolic state. This, of course, is precisely the manner in which an effective regulatory mechanism should operate.

The design of the present experiments was based on our previous observation (12), herein entirely confirmed, that in euthyroid individual pharmacological doses of iodide produce relatively acutely slight decreases in the serum concentrations of both T_4 and T_3. Since iodides inhibit hormone synthesis only transiently, the observed decrease in serum T_4 concentration is best explained by an inhibition of the thyroid proteolytic or secretory process. This explanation may explain in part the iodide-induced decrease in serum T_3 concentration, but a portion is probably also the result of decreased peripheral generation of T_3 secondary to lowering of the serum T_4 concentration. Moreover, some of the decrease in basal serum T_3 concentration induced by iodides may reflect a shift in the relative rates of synthesis of T_4 and T_3, favoring T_4. Nagataki, Uchimura, Masuyama, Nakao, and Ito have demonstrated the T_4/T_3 ratio within thyroglobulin is higher in residents of Japan, who characteristically ingest a diet rich in iodide, than in residents of the United States (18).

Despite a greater rise in serum TSH concentration, the increase in serum T_3 concentration induced by TRH during iodide administration was less than during the control period. As with the lower basal serum T_3 concentration seen during iodide administration, this could reflect either a general effect of iodide to inhibit hormone secretion or a shift in the T_4/T_3 ratio within the thyroid in favor of T_4. Unfortunately, in the present studies, specimens of blood were not taken at a sufficiently long interval after administration of TRH to permit evaluation of the effect of iodide on the response of the serum T_4 concentration, this being best assessed some 6 h after TRH is given (19). Hence, the extent to which iodides may have inhibited the TRH-induced secretion of T_4 could not be evaluated.

Earlier studies have described a group of patients with underlying thyroid disease, be it Hashimoto's disease, simple goiter, or treated Graves's disease, who apparently have mild, compensated thyroid failure or "subclinical hypothyroidism" (20–22). The group is defined by the fact that although the patients are clinically euthyroid and serum T_4 and T_3 concentrations are within the normal range, serum TSH concentration is slightly

elevated. Recently, Evered, Ormston, Smith, Hall, and Bird have demonstrated that patients of this type display a mildly increased response of the serum TSH concentration to exogenous TRH administration (*22*). The results of the present study go beyond this finding in two respects. First, the degree of hormone deficiency that iodides induced, though sufficient to increase basal serum TSH concentrations from control values, was not sufficient to bring them above the normal range. Second, the hormone deficiency which led to increased TRH responsiveness during iodide administration was of short duration, at most 10 days, while the deficit in patients with subclinical hypothyroidism is likely to have been chronic.

The subtlety of the decrease in thyroid hormone supply that enhances response to TRH, and the rapidity with which this change is manifest, suggests that increased responsiveness to TRH within the pituitary may be sufficient to explain the increased secretion of TSH seen in mild or compensated thyroid failure, and that increased secretion of TRH need not be invoked. This conclusion would accord with the fact that hypothalamic TRH content is normal in hypothyroid rats (*23*). However, with respect to both mild and severe hypothyroidism in man, definitive conclusions concerning the relative roles of increased TRH secretion and enhanced pituitary responsiveness in augmenting TSH secretion must await the development of methods for measuring the rate of TRH secretion.

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