Variable Thyrotropin Response to Thyrotropin-releasing Hormone after Small Decreases in Plasma Free Thyroid Hormone Concentrations in Patients with Nonthyroidal Diseases

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A B S T R A C T Although a normal serum thyrotropin (TSH) concentration is generally considered to be the most important finding to support the clinical impression of euthyroidism in patients with nonthyroidal diseases and decreased serum triiodothyronine (T_3), the regulation of TSH secretion in sick patients has not been studied previously. Accordingly, we studied the regulation of TSH secretion in 23 patients with nonthyroidal diseases; 15 of the patients had decreased serum T_3. TSH regulation was studied by measuring the TSH response to injected thyrotropin-releasing hormone (TRH) before and after effecting a small decrease in serum thyroxine (T_4) and/or T_3 concentrations by iodide treatment, 262 mg daily for 10 d. Iodide treatment significantly decreased (>10%) the free T_4 index (FT_4-I) and/or free T_3 index (FT_3-I) in all patients. FT_4-I values were correlated (0.611, $P < 0.001$), with free T_4 concentration determined by equilibrium dialysis. Despite decreased FT_4-I and/or FT_3-I after iodide treatment in all patients, the TSH response to TRH after iodide treatment was augmented in only 8 of 15 patients who had decreased serum T_3 (group 1) and in only 5 of 8 patients who had a normal serum T_3. Mean base-line TSH concentration was increased significantly ($P < 0.05$) from 0.9±0.1 to 1.5±0.3 μU/ml in group 1 only. Comparison of the mean TSH response to TRH showed that there was no significant difference between groups 1 and 2. Moreover, no significant difference in thyroidal parameters was observed between patients who had augmented TSH response to TRH after iodides and those who had either similar or decreased TSH response irrespective of the initial

serum T_3. These studies show that an augmented TSH response to TRH in response to a small reduction in serum T_4 and T_3 concentration occurred in only 57% of the entire group of patients with nonthyroidal diseases and that the presence or absence of a normal TSH response to this stimulus did not seem to be related to the base-line serum T_3 concentration. Because an increase in serum TSH in response to decreased serum T_4 and T_3 did not occur in about one-half of patients with nonthyroidal diseases, normal serum TSH may not be a reliable index of the euthyroid state in these patients.

INTRODUCTION

Changes occur frequently in peripheral thyroid hormone metabolism and in results of tests of thyroid function in patients with acute and chronic nonthyroidal diseases (1–12). Characteristic laboratory data in such patients include normal to slightly decreased serum thyroxine (T_4)[1] concentration and decreased serum T_4 binding. Free T_4 concentration is within the normal range or increased. Decreased serum triiodothyronine (T_3) concentration is found in most patients, and although serum T_3 binding is decreased, free T_3 concentration is generally decreased as well. Inasmuch as it is probable that T_3 affects most of the biological activities of the thyroid hormones in human subjects (13–15), these measurements in sick patients could readily be interpreted as consistent with hypothyroidism. It is interesting, therefore, that on the basis of

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[1] *Abbreviations used in this paper:* FT_3-I, free triiodothyronine index; FT_4-I, free thyroxine index; T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyrotropin.

clinical evaluation, most patients with nonthyroidal diseases are considered euthyroid. The latter interpretation is supported by the consistent finding that serum thyrotropin (TSH) concentration remains within the normal range in most patients. In healthy euthyroid subjects, TSH secretion is very closely regulated by serum thyroid hormone concentrations. Even a small decrease in serum T_4 and T_3 stimulates TSH secretion and increases serum TSH concentration (16, 17). Indeed, an increase in serum TSH is generally considered to be the most sensitive indicator of hypothyroidism due to thyroid disease (18, 19). Although normal serum TSH concentration provides the principal laboratory evidence to support the diagnosis of euthyroidism in these patients, the regulation of TSH secretion by thyroid hormones in patients with nonthyroidal diseases has not been examined. The possibility exists, for example, that a decrease in thyroid

hormone concentrations in these patients does not increase TSH secretion and serum TSH concentration. If so, sick patients with decreased serum T_3 might be hypothyroid despite normal serum TSH concentrations.

METHODS

Studies of TSH secretion were carried out in 12 male and 11 female patients hospitalized with nonthyroidal diseases at Montefiore Hospital and Medical Center or in Beth Abraham Hospital, Bronx, New York (Table I). Most patients suffered from neoplastic diseases, but several had cerebrovascular or hepatic disorders. Each subject was informed of the nature of the study and gave informed and written consent according to institutional guidelines. Patients with a history of thyroid disorders or medications were excluded from the study, as were patients with thyroid enlargement, renal failure, or those treated with corticosteroid or estrogenic medications. Patients who were severely malnourished or

TABLE I

Effect of Iodide Administration on the Plasma Concentration of T_4, T_3, and TSH in Patients with Nonthyroidal Diseases

		Patient				T_4*		FT_4-I		T_3		FT_3-I		TSH	
	Number	Initials	Age	Sex	Diagnosis	C	I	C	I	C	I	C	I	C	I
			yr			*μg/dl*				*ng/dl*				*μU/ml*	
Group 1	1	R.A.	81	F	Carcinoma of ovary	10.2	10.9	10.2	8.7	39	26	41	29	0.9	3.1
Decreased	2	C.K.	75	M	Carcinoma of lung	9.0	7.9	8.8	6.9	45	42	44	41	0.6	3.4
serum T_3	3	M.K.	76	F	Cerebrovascular accident	7.6	6.2	8.0	5.7	75	65	60	53	1.7	1.8
	4	J.R.	78	F	Cerebrovascular accident	9.0	7.5	6.1	5.5	99	71	64	64	0.6	0.6
	5	E.C.	79	F	Carcinoma of breast	6.0	7.0	12.8	9.5	39	53	88	81	0.6	1.3
	6	C.DeT	62	F	Carcinoma of breast	9.7	8.1	8.5	6.0	91	122	80	80	1.3	2.5
	7	M.S.	69	F	Carcinoma of breast	7.1	6.5	3.4	2.9	97	97	45	34	0.6	1.8
	8	L.L.	72	F	Cerebrovascular accident	8.3	8.3	9.7	5.9	71	69	60	57	0.6	1.6
	9	R.S.	76	F	Fever unknown origin	9.0	6.8	6.4	5.4	89	65	63	52	0.8	0.6
	10	G.G.	58	M	Carcinoma of lung	7.3	6.5	7.0	4.9	49	55	42	53	0.6	0.6
	11	J.K.	70	M	Carcinoma of lung	6.8	8.6	8.1	7.5	66	67	63	49	1.1	0.6
	12	H.K.	76	M	Diabetes mellitus	5.0	3.7	4.5	4.2	84	75	52	51	1.1	0.9
	13	T.A.	27	M	Laennec's cirrhosis	6.0	5.5	9.9	6.5	47	56	69	55	1.9	1.8
	14	D.W.	50	M	Carcinoma of esophagus	9.1	6.4	12.6	7.1	48	40	60	45	0.6	0.6
	15	C.G.	70	M	Carcinoma of mandible	10.0	6.3	9.4	9.2	50	39	61	53	0.8	0.6
Mean			67.9			8.0	7.1	8.4	6.4	65.9	62.8	59.5	53.1	0.9	1.5
SEM (±)			4.6			0.4	0.4	0.7	0.5	5.7	6.2	3.5	3.7	0.1	0.3
P						<0.025		<0.001		<0.001		<0.005		<0.05	
Group 2	16	C.H.	68	F	Carcinoma of breast	10.5	12.8	8.5	8.2	152	163	125	105	0.6	1.9
Normal	17	C.M.	56	F	Carcinoma of breast	7.9	7.5	6.7	5.2	129	106	110	73	2.0	3.6
serum T_3	18	F.G.	57	M	Carcinoma of sinuses	9.3	5.8	12.7	5.8	140	124	115	106	1.0	2.9
	19	I.P.	43	M	Carcinoma of lung	9.7	9.1	8.0	9.1	112	116	123	109	1.6	3.7
	20	A.S.	82	M	Carcinoma of lung	6.2	6.7	4.9	5.2	176	139	139	108	0.6	3.3
	21	M.DeS.	49	M	Hypernephroma	6.4	8.3	7.6	7.8	106	94	109	88	1.6	0.6
	22	J.G.	46	F	Carcinoma of breast	10.4	10.0	11.7	9.3	116	91	120	85	0.6	0.6
	23	F.G.	77	M	Carcinoma of esophagus	8.6	5.4	9.0	5.4	133	69	140	97	1.5	1.4
Mean			59.5			8.6	8.2	8.6	7.0	133.0	112.8	122.6	96.4	1.2	2.3
SEM (±)			7.2			0.6	0.9	0.9	0.6	8.2	10.5	4.2	4.6	0.2	0.5
P						NS		NS		<0.05		<0.001		NS	
Group 1 vs. group 2　P			<0.05			NS	NS	NS	NS	<0.001	<0.001	<0.001	<0.001	NS	NS

* Each value represents the average of two or three determinations during the control period (C) or after iodide treatment (I), 262 mg daily for 10 d. The limit of detection for serum TSH is 0.6 μU/ml for most assays. All TSH determinations in the undetectable range were assigned a value of 0.6 μU/ml to facilitate statistical analysis. Group 1 contained patients with decreased serum FT_3-I; patients in group 2 had FT_3-I concentration within the normal range. Statistical analysis was done by paired t tests for comparisons between the control period and after iodide treatment. Two-tailed (independent) t tests were done to compare the mean values for each parameter of group 1 with those of group 2.

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who appeared moribund were not selected for this study. Two patients, 10 and 11, were moderately cachetic at the initiation of the study and died ~2 mo and 2 wk, respectively, after the study was completed. Patient 21 was placed on cancer chemotherapy during the study. All other patients were stable without specific new treatment during the study. Assessment of patient status 4 mo after the study was completed revealed that patients 1 and 20 died 2 and 4 mo, respectively, after the study was completed. The remaining 19 patients were being monitored by the oncology clinic or were permanent residents of Beth Abraham Hospital for their chronic illness.

Studies of TSH secretion in response to small decreases in plasma thyroid hormone concentrations were carried out according to the general procedures described by Vagenakis et al. (16) and Saberi and Utiger (17). Serum was obtained for measurement of thyroid hormone concentration, binding, and TSH concentration on 2 control days. On the 2nd control day, blood was obtained at −10, 0, 10, 20, 30, 60, and 120 min after an intravenous bolus injection of 500 μg thyrotropin-releasing hormone (TRH) (Thypinone, Abbott Diagnostics, Diagnostic Products, North Chicago, Ill.) as previously described (20). All patients were then treated with iodides, 262 mg I⁻/d, in the form of supersaturated potassium iodide, 8 drops (1 drop = 0.05 ml) per os twice each day for 10 d. Blood samples for hormone measurements were obtained on the 5th, 7th, and 9th days of iodide treatment. On the 10th day, two samples were obtained and a second TRH test was performed. Serum was obtained rapidly by centrifugation and stored frozen at −20°C until required for hormone assays. Duplicate measurements of all samples for each patient were carried out in the same assay.

Hormone concentrations were measured by radioimmunoassay. Serum T_4 concentration was measured by the Corning method (Immophase, Corning Medical, Corning Glassworks, Medfield, Mass.); the normal range was 4.5–12.0 μg/dl. Serum T_3 was measured as previously described (21); the normal range was 90–180 ng/dl. Serum TSH concentration was measured by modifications of the double-antibody technique of Odell et al. (22), as described previously (3, 20). Human TSH and TSH antiserum were gifts from the National Pituitary Agency of the National Institutes of Health, and human TSH Standard 68/38 was a gift of the Division of Biological Standards, National Institutes of Medical Research, Mill Hill, London. The limit of detectability in the TSH assay was generally 0.6 μU/ml, and the normal range was <0.6–5.0 μU/ml. At the present time, ~50% of subjects without thyroid disease have undetectable TSH in our laboratory. For the three hormone measurements, the intraassay coefficients of variation were 5.7% for T_4, 6.3% for T_3, and 11.3% for TSH.

The intensity of hormone binding by serum proteins was determined by the Res-Q-Mat T_3 Micro Test (Mallinckrodt Inc., St. Louis, Mo.). Free/bound ratios were calculated and corrected for interassay variability using the free/bound ratios for two control pools of serum that were measured concurrently with the unknowns, as previously described (23). The corrected free/bound ratio was divided by the mean free/bound ratio for control patients to yield a binding index, and the product of the binding index and the T_4 or T_3 concentration was defined as the free T_4 index (FT$_4$-I) or free T_3 index (FT$_3$-I). Plasma free T_4 concentration was also determined by equilibrium dialysis (BioScience Laboratories, Van Nuys, Calif.; normal range was 1.0–2.3 ng/dl) in a single plasma sample obtained from each patient during the control period.

Patients were grouped according to their base-line FT$_3$-I and response to TRH as outlined in Table I. Data for the various groups were expressed as a mean±SEM. Statistical analysis was by two-tailed t test or by t tests of paired observations when appropriate (24).

RESULTS

The clinical and laboratory data in the control period and after iodide therapy are listed in Table I. The age range of the patients was between 27 and 82 yr and the mean age of the entire group was 65.0 yr. Despite the fact that all patients appeared euthyroid clinically, serum T_3 or FT$_3$-I were decreased to values below the normal range in 15 of the 23 patients (Table I), patients 1–15 (group 1). Although the range in age was wide, the mean age of patients with decreased T_3, 67.9±4.6 yr, was significantly greater than the mean age of the eight patients with normal serum T_3 (group 2), 59.5±7.2 yr (P < 0.05). None of the patients studied was moribund or severely malnourished as judged by clinical evaluation. Four patients died after the study was completed: patient 11, after 2 wk; patients 1 and 10, after 2 mo; and patient 20, after 4 mo. Aside from the decrease in mean T_3 and FT$_3$-I in patients in group 1, no significant difference in any of the other parameters of thyroid function was observed between group 1 and group 2 (Table I). Free T_4 concentration determined by equilibrium dialysis was correlated with FT$_4$-I measurements, r = 0.611, P < 0.001. The mean free T_4 concentration of group 1, 2.0±0.4 ng/dl, was not significantly different from group 2, 2.7±0.4 ng/dl. The TSH response to TRH during the control period was also similar (Fig. 1, filled symbols). A significant difference between the groups was noted only at 10 min after TRH injection. The mean serum TSH at that time for group 2, 5.1±1.3 μU/ml, was significantly greater than that of group 1, 2.2±0.4 μU/ml, P < 0.025. Moreover, there was no difference in the mean integrated TSH response to TRH between the two groups.

Treatment with iodide decreased mean serum T_4 in all groups, but this change was significant statistically for group 1 only (Table I). Similarly, mean serum FT$_4$-I decreased significantly after iodide therapy only in group 1. Mean serum T_3 concentration and FT$_3$-I decreased after iodide treatment in most patients and a significant decrease in mean serum T_3 and FT$_3$-I was noted in both groups after iodide treatment. Treatment with iodide resulted in a 10% or greater decrease either in FT$_4$-I and/or FT$_3$-I in all patients (Table I).

A small increase in mean base-line serum TSH was observed after iodide treatment in both groups, but the increase was significant statistically (P < 0.05) only in group 1 (Table I). The TSH response to TRH before and after iodide treatment is shown in Fig. 1. As indicated in the lower panel for the patients with normal serum T_3 (group 2), the TSH response to TRH after treatment was not different statistically from the response before treatment. Similar results
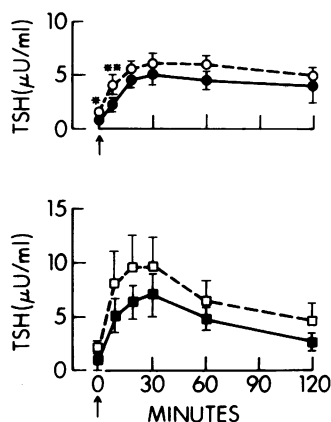
FIGURE 1 Effect of iodide on the TSH response to TRH in patients with nonthyroidal diseases. TRH (500 μg) was injected i.v. during the control period and after 10 d of iodide treatment, 262 mg I/d. The upper panel shows the mean±SEM serum TSH after TRH for group 1 patients in whom the serum T_3 was decreased, and the lower panel shows similar data for group 2 patients who had serum T_3 within the normal range. The vertical arrows indicate the time of TRH injection. Filled symbols and continuous lines indicate TSH data before iodide treatment, and open symbols and interrupted lines indicate TSH data after iodide treatment. * $P < 0.05$; ** $P < 0.025$.

were obtained for the group with decreased serum T_3 (Fig. 1, upper panel) although the base-line and 10-min mean value for serum TSH was minimally but significantly increased after iodide treatment. There was no difference in the mean integrated TSH response to TRH after iodide treatment for either group.

Examination of individual patients' responses to TRH showed that 8 of the 15 patients in group 1 and 5 of the 8 patients in group 2 had the anticipated increase in TSH response to TRH after iodide treatment. To determine whether patients with an appropriate increase in TSH response to TRH after treatment could be identified on the basis of other thyroidal parameters, we analyzed statistically the parameters listed in Table I for subgroups within groups 1 and 2. No significant differences in mean serum T_4, FT_4-I, T_3, or FT_3-I were evident between groups of patients who exhibited an augmented TSH response to TRH after iodide treatment and those who had either the same or a decreased TSH response to TRH after treatment in groups 1 and 2. Our results do not provide a guide for selection of patients who respond appropriately to iodide treatment.

DISCUSSION

Our studies suggest that there is abnormal regulation of TSH secretion in many patients with nonthyroidal diseases and that a normal TSH concentration may not be a valid index of the euthyroid state, as considered

previously. Despite the decrease in serum T_3 and FT_3-I, and variable changes in serum T_4 and FT_4-I, serum TSH and the TSH response to TRH have been normal in most reports of patients with nonthyroidal diseases (1–12). However, Bermudez et al. (3) showed that a small increase in the TSH response to TRH occurred in sick patients with decreased serum T_3 as compared with similar patients with serum T_3 in the normal range; and Burroughs et al. (11) reported that the TSH response to TRH was blunted in about one-third of euthyroid geriatric patients with a variety of nonthyroidal diseases. A principal question raised in all of these studies is whether or not patients with nonthyroidal diseases and decreased serum T_3 are euthyroid. Euthyroidism could be sustained (a) by downward regulation of the thyrotroph set point for T_3 so that, despite decreased serum and pituitary T_3, TSH secretion remains normal; (b) by an increase in the intrapituitary conversion of T_4 to T_3, resulting in normal pituitary T_3 despite decreased serum T_3 concentration; or (c) by a combination of these changes.

Irrespective of the underlying biological mechanisms, it seems clear that if euthyroidism is maintained in these patients, TSH secretion should be responsive to small changes in serum thyroid hormone concentrations in a fashion similar to healthy controls. In normal subjects, Vagenakis et al. (16) and Saberi and Utiger (17) have shown that a small reduction in serum T_4 and T_3 concentration after iodide treatment augments basal and TRH-induced TSH release. Conversely, a small elevation of T_4 and T_3 concentrations, with values still within the normal range, decreases the TSH response to TRH (25). The close regulation of TSH secretion by thyroid hormones also occurs in some patients with decreased serum T_3. In normal subjects with decreased serum T_3 after a short-term fast, Gardner et al. (26) showed that TSH secretion is augmented after iodide treatment and suppressed after T_3 supplementation in a manner similar to controls. Because these changes in TSH secretion were demonstrated with T_3 concentrations within the normal range (in the case of T_3 supplementation) or with only a small decrease in serum T_3 below that already present in the fasted state, the authors suggested that the set point for TSH secretion was decreased in these patients and that, even at the lower set point, TSH secretion was normally sensitive to small changes in thyroid hormone concentrations.

Although we did not test the sensitivity of TSH secretion to suppression by administered thyroid hormones, 10 of 23 patients studied in this investigation failed to augment TSH secretion in response to a small decrease in FT_3-I and FT_4-I induced by iodide treatment. Because determination of thyroidal state was a principal focus of these studies, we grouped our patients according to the serum FT_3-I concentration. For groups of

patients with either normal or decreased serum T_3, the mean TSH response to TRH after iodide treatment was not significantly different from the TSH response before iodides. 53% of patients with decreased FT_3-I and 63% of patients with normal FT_3-I failed to augment TSH secretion after iodide. Thus, on the basis of these studies, abnormal TSH regulation seemed to be unrelated to serum T_3 concentration in patients with nonthyroidal disease. Those patients who did not augment TSH secretion after iodide consisted of eight males and two females. Although the groups are small, the disproportionate sex distribution suggests that abnormal regulation of TSH secretion may be more common in sick male than in sick female patients. Although TSH responsiveness after iodide has not been studied as a function of age or sex, published reports indicate that the TSH response to TRH may be decreased in elderly males (27). In our studies, the TSH responders and nonresponders after iodide could not be distinguished on the basis of age, serum T_4, or FT_4-I concentrations, or on our clinical impression of the severity of the illness. Decreased serum TSH concentration and TSH response to TRH have been reported in some studies of short-term fasting, (28, 29) but these findings do not appear to be consistent, as pointed out by Gardner et al. (26). The inability of some patients with nonthyroidal diseases to augment TSH secretion in response to decreased serum FT_4-I and FT_3-I after iodide suggests altered regulation of TSH secretion, and raises the possibility that such patients might not be able to increase TSH secretion in response to decreased serum thyroid hormone concentrations due to thyroid failure. Thus, the lack of an increase in serum TSH concentration may not be taken as clear-cut evidence for euthyroidism in all patients with nonthyroidal diseases who have decreased serum T_3.

The results of our study complicate the interpretation of the already confusing laboratory findings in patients with nonthyroidal diseases. Earlier studies indicated that although serum protein-bound iodine was decreased, serum free T_4 concentration was either normal or increased, and the free T_4 concentration was considered to support the interpretation of euthyroidism. The more recent finding of a decreased serum T_3 in sick patients again raises the possibility of underlying hypothyroidism in these patients, but a normal serum TSH concentration has been interpreted to indicate that the pituitary at least is euthyroid. Our studies suggest that the normal serum TSH may not be a reliable index for the euthyroid state in all patients. An additional feature that warrants consideration is the fact that the diagnosis of primary hypothyroidism is occasionally made in patients who also have nonthyroidal diseases. Serum TSH concentration is appropriately increased in such patients, although it may be argued that the magnitude of the serum TSH might be

greater in the absence of the nonthyroidal disease. Thus it is likely that most patients with nonthyroidal diseases who also have significant primary hypothyroidism would have sufficient symptoms and signs of hypothyroidism to suggest the diagnosis, and that the diagnosis would be supported by an elevation in serum TSH. Until a biological measure of thyroidal activity is developed that is not influenced by other factors that occur in nonthyroidal diseases, it would still appear prudent to rely on clinical evaluation as well as an increase in serum TSH to establish a diagnosis of primary hypothyroidism in these patients.

ACKNOWLEDGMENTS

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