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Serum Thyrotropin Responses to Synthetic Thyrotropin-Releasing Hormone in Normal Children and Hypopituitary Patients. A NEW TEST TO DISTINGUISH PRIMARY RELEASING HORMONE DEFICIENCY FROM PRIMARY PITUITARY HORMONE DEFICIENCY

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Research Article

Synthetic thyrotropin-releasing hormone (TRH) was administered intravenously in a dose of 7 μg/kg to 20 normal children ages 4-13 yr. Serum thyroid-stimulating hormone (TSH) was measured by radioimmunoassay and rose from a mean value of 1.7 μU/ml (range = < 1.25-7.2) to a mean peak value of 21.5 μU/ml (5.2-33.2) at 15 or 30 min after administration.

13 patients with idiopathic hypopituitarism and apparent normal thyroid function, ages 3-19 yr, responded to TRH in a manner very similar to the control subjects: TSH rose from a mean value of 1.8 μU/ml (range < 1.25-4.3) to a mean peak value of 18.5 μU/ml (range = 9.5-45.0) which occurred between 15 and 60 min after TRH.

13 idiopathic hypopituitary patients with documented thyroid deficiency were tested after thyroid therapy had been discontinued for a minimum of 10 days. The serum TSH values in 10 of 13 patients rose from a mean base line level of 2.2 μU/ml (< 1.25-5.3) to a peak mean value of 32.5 μU/ml (9.6-61.3) between 30 and 120 min after TRH. In three patients, however, little or no TSH response was detected, even when serum thyroxine levels were extremely low. Similar to the latter group, three of five patients with hypopituitarism secondary to craniopharyngiomas had undetectable or barely measurable TSH levels before and after TRH. Two of these […]

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ABSTRACT Synthetic thyrotropin-releasing hormone (TRH) was administered intravenously in a dose of 7 μg/kg to 20 normal children ages 4–13 yr. Serum thyroid-stimulating hormone (TSH) was measured by radioimmunoassay and rose from a mean value of 1.7 μU/ml (range = < 1.25–7.2) to a mean peak value of 21.5 μU/ml (5.2–33.2) at 15 or 30 min after administration.

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Side effects were experienced in 41 of 54 patients (76%). The effects were limited to a mild nausea-like sensation in 63% of the patients and occurred within the first 5 min after receiving TRH. No evidence of serious toxicity or long-term side effects was noted.

The TRH test is a safe, effective way to measure TSH reserve in children. The positive response in 10 of 13 patients with secondary hypothyroidism supports data previously accumulated that most patients with idiopathic hypopituitarism have an abnormality of their hypothalamic-releasing hormone function, whereas the remaining minority probably have primary pituitary disease.

INTRODUCTION

Since thyrotropin-releasing hormone (TRH)[1] was determined to be pGlu-His-Pro-NH_2 (1, 2), synthetic TRH has been prepared for clinical investigation and

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[1] *Abbreviations used in this paper:* EP-AITT, epinephrine-propranolol infusions during insulin-arginine tolerance test; FT4, free thyroxine concentrations; GH, growth hormone; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; T4, serum thyroxine iodine concentrations; 17-OHCS, 24 hr urinary excretion of 17-hydroxycorticosteroids.

has proven to be a potent stimulator for the release of human pituitary thyrotropin (TSH) in adults (3–12). In order to develop a test of pituitary TSH reserve in children, we studied the effects of intravenous synthetic TRH upon the serum TSH concentrations in normal children and hypopituitary patients.

METHODS

Subjects. 20 normal children with no apparent thyroid or pituitary disease were studied. This group was comprised of 7 males and 13 females between the ages of 4 and 13 yr. 31 hypopituitary patients selected from our clinic who fulfilled the criteria for diagnosis (13, 14) were also studied. Seven of the idiopathic hypopituitary patients also received epinephrine-propranolol infusions during an insulin-arginine tolerance test (EP-AITT), as previously described (15), to ascertain if a correlation could be made between the responses to these stimuli and to TRH.

The patients were divided into four major groups: group I, normal children and adolescents; group II, children with idiopathic hypopituitarism and normal thyroid function; group III, same as group II except with deficient thyroid function; and group IV, children with "organic" hypopituitarism—i.e., secondary to a tumor in or proximal to the pituitary.

Methods. In performing the TRH study, patients were tested after an overnight fast. Blood was obtained at −20 and 0 min, after which time 7 μg/kg of synthetic TRH[2] were administered intravenously over 60 sec. Blood samples were subsequently obtained from an indwelling needle at 15, 30, 45, and 60 min in all subjects, and at an additional 90 and 120 min after TRH in the hypopituitary patients. Blood was obtained in 20 normal patients before TRH and at 24 hr after TRH for thyroid function tests, chemistries using the channel 12 AutoAnalyzer,[3] and complete blood count. The same studies were performed at 0 and 120 min after TRH in the hypopituitary patients. Since serum TSH cannot be measured in approximately 40% of normal subjects, we utilized a value of 0.7 μU/ml for calculations of values that fell below the sensitivity of the assay, which is 1.25 μU/ml.

Serum thyroxine iodine concentrations (T4) by column and free thyroxine concentrations (FT4) were determined by a commercial laboratory.[4] Since the lowest T4 concentration in these 20 patients was 3.6 μg/100 ml and the lowest free T4 concentration was 1.3 ng/100 ml, we accepted a diagnosis of thyroxine deficiency only if these two values were less than 3.4 μg/100 ml and 1.2 ng/100 ml respectively.

The TSH radioimmunoassay was performed as previously described (16). All samples were measured in triplicate. The coefficient of variation for intra-assay variability assessed in the hypothyroid and normal range of the standard curve was 14.1 and 4.1% respectively. Blood samples for TSH were stored at −20°C until assayed. The Human Thyrotropin Research Standard A (HTRS) was used as standard.[5]

The Piromen stimulation and cortisol and growth hormone (GH) concentrations resulting from this stimulation were performed as previously described (17, 18).

RESULTS

Normal children

Group I. All but one patient responded to TRH with levels of TSH which are found in hypothyroid patients—i.e., greater than 7 μU/ml. The peak level of TSH occurred at 30 min after TRH in 14 of the 20 children, and at 15 min in the remaining 6 patients. Serum TSH levels rose from a mean value of 1.7 ±1.8 μU/ml (SD) to a mean peak value of 21.5 ±8.3 μU/ml (SD) (Table I, column 1). The one patient whose TSH rose to only 5.2 μU/ml did demonstrate a fivefold rise (1–5.2 μU/ml). Two children also received 1.9 and 2.6 μg/kg of synthetic TRH (total doses: 50 and 80 μg), and had TSH responses similar to those obtained with a dose of 7 μg/kg (184 and 188 μg).

No significant change in mean serum thyroxine-iodine (T4) and free thyroxine concentrations (FT4) occurred at 24 hr after TRH.

Side effects occurred in 14 of the 20 normal subjects and were limited to a 5-min period after TRH administration. According to our grading system of the type and severity of clinical side effects,[6] only eight patients experienced side effects graded as 2+. No side effects of grade 3+ or 4+ severity were experienced among normal children. No significant or consistent alterations of 12 routine, chemical blood determinations performed by AutoAnalyzer or of the complete blood count were observed.

Hypopituitary patients

Group II. Of the 13 patients in group II with idiopathic hypopituitarism, the serum TSH after TRH was significantly elevated in all patients, and rose from a mean value of 1.8 ±1.2 μU/ml (SD) to a mean peak value of 18.5 ±10.0 μU/ml (SD) (Table I, column 2). The peak TSH level occurred at 30 min after TRH in

[2] Kindly supplied by Dr. Michael S. Anderson, Associate Director, Department of Clinical Research, Abbott Laboratories, North Chicago, Ill., and administered only after informed, signed parental consent.

[3] SMA 12/60, Technicon Corporation, Ardsley, N. Y.

[4] Bioscience Laboratories, Van Nuys, Calif.

[5] Kindly supplied by the World Health Organization, International Laboratories for Biological Standards, National Institute for Medical Research, Mill Hill, London, England.

[6] Classification of clinical side effects: grade 0, no symptoms experienced or measured; grade 1+, mild nausea-like sensation; grade 2+, nausea with mild degree of facial flushing, hot sensation, and/or urge to void; grade 3+, above symptoms of more intensity with slight elevation of blood pressure and pulse (less than 10 mm Hg blood pressure or 20% increase in pulse); grade 4+, all of the above symptoms and signs with the patient very uncomfortable and vomiting. (The latter occurred in only one patient.)

10 of the 13 patients, and at 15, 45, and 60 min after TRH in the remaining 3 patients, (Table II).

In one patient who received a 30-min infusion of TRH on the 3rd day after the standard test, there was a similar TSH response, although the peak and serial serum TSH levels were consistently higher in response to the 30-min infusion (Table II).

The mean T4 and free T4 before TRH were 4.4 ±0.6 μg/100 ml (SD) and 1.7 ±0.3 ng/100 ml (SD) respectively, and did not rise significantly (4.8 ±0.8 μg/100 ml and 2.0 ±0.4 ng/100 ml) at 120 min after TRH.

Group III. Among the 13 idiopathic hypopituitary patients with thyroid deficiency in this group, 10 (designated group III A) had significant serum TSH responses to TRH in that the serum TSH rose from a mean of 2.2 ±1.6 μU/ml (SD) to a mean peak value of 32.5 ±16.3 μU/ml (SD) (Tables I and II). Although the range was wide, the mean peak TSH for the 10 patients in group III A was significantly higher than for either group I or group II patients (Table I). The peak TSH responses occurred between 30 and 120 min after TRH (Table II). Although the mean T4 and FT4 concentrations of the group III A patients were significantly lower than either the group I or group II patients, the mean T4 and FT4 concentrations for patients in group III A before (2.3 ±0.6 μg/100 ml SD and 0.8 ±0.1 ng/100 ml) SD and at 120 min after TRH (2.5 ±0.8 μg/100 ml SD and 0.9 ±0.3 ng/100 ml SD) were not significantly different ($P > 0.2$ and > 0.3).

In contrast to patients in group III A, three idiopathic hypopituitary patients with decreased thyroid function and, therefore, apparent TSH deficiency (designated group III B), exhibited little or no rise in serum TSH after TRH (Table II). All patients in group III who previously had received exogenous, thyroid hormone replacement were off medication for at least 10 days before testing.

Group IV. Four of the five patients in group IV had undergone pituitary surgery for the removal of a craniopharyngioma at least 6 months before the test. Of these four patients, two (K. S. and R. G., Table II) had no measurable TSH (designated as 0.7 μU/ml) at any time before or after TRH; one (D. Y.) had a slight but insignificant TSH response; and one (T. H.) responded normally to TRH. One patient (L. M.) had tests that revealed an intrasellar, calcified mass indicative of a craniopharyngioma, but received TRH before any surgical procedure was considered. Her TSH response to TRH was normal. As noted in Table II, all of these patients with the exception of L. M. and including T. H. had markedly decreased thyroxine values.

Hypopituitary patients in general exhibited similar side effects as those observed in the normal children. Of the 31 hypopituitary patients studied, 7 (23%) had no side effects. In the remaining 24 patients, 13 had symptoms classified as grade 1, 5, as grade 2, 4, as grade 3, and 2 as grade 4.

TABLE I

Serum TSH Responses to Synthetic TRH

	Group I	Group II	Group III A
Base line TSH, *μU/ml*			
Mean	1.7	1.8	2.2
Range	<1.2–7.2	<1.2–4.3	<1.2–4.6
1 SD	1.8	1.2	1.6
1 SEM	0.3	0.2	0.4
Peak TSH, *μU/ml*			
Mean	21.5	18.5	32.5
Range	5.2–33.3	9.5–45.0	9.6–61.3
1 SD	8.3	10.0	16.3
1 SEM	1.9	2.8	5.2
P values	Group I vs. II	Group I vs. III A	Group II vs. III A
Base line TSH	>0.4	>0.1	>0.1
Peak TSH	>0.1	<0.05	<0.05

Miscellaneous group

In addition to the above groups, a patient with acquired juvenile hypothyroidism and elevated serum TSH values, and a euthyroid patient with a posttraumatic hypothalamic lesion associated with sexual precocity plus obesity, responded to TRH with increased TSH levels.

Correlations between pituitary hormone responses to Piromen, epinephrine-propranolol + arginine-insulin infusions, and TRH

These tests have been done in some of the patients who received TRH (11, 12, 15). These data are presented in Table III.

11 of the patients in groups II, III, and IV received piromen as a stimulus for cortisol and GH production (17, 18). All nine of the patients with idiopathic hypopituitarism (groups II and III) responded normally with a significant increase in 17-OHCS production, although all nine previously had failed to respond to Metopirone with an increase in 17-OHCS production (17, 18). The two patients with organic hypopituitarism who received Piromen failed to respond normally (group IV, Table III). However, none of the patients responded normally to Piromen with an increase in GH concentrations (18), and none of the six patients with idiopathic hypopituitarism, who received propranolol and epinephrine in conjunction with arginine and insulin, responded with the normal augmentation of GH

TABLE II

Mean Base Line and Peak Serum TSH in Individual Patients after Synthetic TRH Administration

Patient	C. A.	TRH dose	Serum TSH: Mean base line	Serum TSH: Peak	Serum TSH: Time, at peak	T4	FT4	Pituitary hormone deficiencies: GH	Pituitary hormone deficiencies: ACTH (SU4885)	Pituitary hormone deficiencies: LH/FSH
	yr	*μg*		*μU/ml*		*μg/100 ml*	*ng/100 ml*			
Group II, idiopathic hypopituitary (IH) patients with normal thyroid function										
C. B.	3.4	80	0.7	18.4	30	4.8	2.5	A	ND	?
F. M.	7.6	100	3.5	16.9	15	4.3	1.7	A	ND	?
S. B.	7.8	123	1.6	11.5	30	4.8	2.0	A	A	?
S. C.	10.0	145	1.5	17.3	30	4.9	1.9	A	N	?
M. H.	11.9	100	3.0	9.5	60	3.6	1.4	A	A	?
G. S.	12.5	270	0.7	9.8	30	5.2	2.0	A	A	?
L. L.	14.7	310	0.7	19.0	45	3.5	1.2	A	A	?
T. L.	15.5	200	0.7	10.7	30	3.9	1.7	A	A	?
T. L.‡	15.5	200	0.7	20.8	30	3.9	1.7	A	A	?
C. S.	15.6	290	3.1	26.5	30	3.4	1.3	A	N	?
C. D. B.	15.6	345	2.5	18.0	30	4.8	1.7	A	N	N
B. S.	16.4	271	0.7	9.8	30	5.0	1.5	A	A	N
R. B.	17.9	390	2.0	27.6	30	4.4	1.6	A	A	N
J. P.	19.3	330	2.7	45.0	30	4.5	1.6	A	A	N
Group III, IH patients with abnormal thyroid function										
III A, responders to TRH										
J. McC.	7.0	140	2.4*	34.6	120	2.5	1.0	A	A	?
L. B.	7.6	145	4.3*	44.1	45	2.3	0.8	A	A	?
E. T.	8.9	153	1.7*	21.3	90	2.1	0.9	A	A	?
M. McQ.	12.0	254	2.1*	30.3	30	2.9	1.0	A	ND	?
P. H.	16.3	364	0.7	14.0	90	2.9	0.9	A	N	N
H. S.	17.8	350	5.2*	48.8	30	2.2	0.9	A	A	N
Da. B.	18.1	305	0.7	9.6	30	0.9	0.6	A	N	N
Do. B.	22.9	255	0.7	21.7	120	2.9	0.8	A	A	A
W. E.	27.3	384	4.2*	61.3	60	2.3	0.8	A	A	A
D. R.	27.3	380	1.2*	38.8	60	1.6	0.6	A	A	A
III B, nonresponders to TRH										
M. S.	13.0	250	0.7	0.7	—	1.4	0.6	A	A	?
M. L.	21.3	377	0.7	2.8	30	0.3	0.2	A	A	A
W. B.	23.3	210	0.7	0.7	—	0.2	0.2	A	A	A
Group IV, organic hypopituitary patients										
D. Y.	6.4	175	0.7	3.0	90	2.0	0.5	A	ND	?
K. S.	10.0	175	0.7	0.7	—	0.5	0.3	A	A	?
R. G.	10.3	140	0.7	0.7	—	0.6	0.4	A	A	?
T. H.	18.8	435	4.9	14.8	30	0.1	0.2	A	A	A
L. M.	17.2	325	1.5	22.5	30	3.8	1.2	A	A	A

* Relative TSH deficiency exists since thyroxin levels are in hypothyroid range and TSH remains in normal range.

‡ Synthetic TRH was given intravenously in physiological saline over 30 min.

N, normal; A, abnormal; ND, not done; ?, too young to determine.

Abnormal: GH, less than 6 ng/ml of immunoreactive GH in response to both arginine and insulin tolerance test (14); ACTH, less than 4.5 mg/m² per day of urinary 17-hydroxycorticoid excretion on the day of or day after Metopirone (19); LH/FSH, serum determinations below that expected for Tanner stage II of adolescence (20).

release (15). Of the nine patients with idiopathic hypopituitarism who responded to Piromen with increased cortisol production, all except M. S. in group III B, responded with increased TSH secondary to TRH stimulation. This patient was a severely affected hypopituitary patient of 13.1 yr who had been treated

TABLE III

Comparison of Patients in Groups I, II, III, and IV

Group	Patient	Sex	17-OHCS response to Piromen	GH augmentation with EP-AITT	TSH response to TRH
I	H. S.	F	N (17)	ND	N
	J. H.	F	ND	N	N
	K. W.	M	ND	N	N
	J. R.	M	ND	N	N
	B. Y.	F	ND	N	N
II	R. B.	M	N (17–18)	ND	N
	B. S.	M	N (17–18)	A	N
	J. P.	M	N (18)	ND	N
	C. B.	M	N (18)	ND	N
	M. H.	F	N (18)	ND	N
	T. L.	M	ND	A	N
	L. L.	M	ND	A	N
	C. S.	M	ND	A	N
III A	Da. B.	M	N (18)	A	N
	W. E.	M	N (17)	ND	N
	Do. B.	F	N (18)	ND	N
	M. McQ.	M	ND	A	N
III B	M. S.	F	N (18 as P. S.)	ND	A
	M. L.	M	ND	A	A
IV	R. G.	M	A (18)	ND	A
	K. S.	F	A (18)	ND	A

Comparison of patients in groups I, II, and III in regard to their plasma 17-hydroxycorticoid response to pyrogen, their growth hormone response to arginine-insulin tolerance test (AITT), and augmentation in response to the addition of epinephrine-propanolol infusions (E-P AITT), and their TSH response to synthetic TRH. The brackets with the pyrogen test results refer to the publications of the response of that patient to pyrogen.

N, normal response; ND, not done; A, abnormal response.

with thyroid replacement for 3.5 yr, whose thyroid replacement was discontinued 10 days before TRH stimulation, and whose T4 by column was 1.4 μg/100 ml and free T4 was 0.6 ng/100 ml at the time of testing. Her TSH concentrations after TRH stimulation were consistently < 1.25 μU/ml.

As expected, the two patients in group IV who had both Piromen and TRH stimulation responded to neither.

Response of other tropic hormones to TRH

Plasma GH and Cortisol were tested for in the serum samples of many of the patients responding to TRH. In no instance did the data indicate that growth hormone or adrenocorticotropin (ACTH) were released as result of the TRH stimulus.

DISCUSSION

The first purpose of this study was to determine if children respond to TRH similarly to adults. This was demonstrated unequivocally. The peak responses in the normal children were quantitatively and temporally similar to those observed in normal adults (3–12). Our observations confirm those reported in children (21, 22). We did not find an increase above base line in T4 and free T4 at 120 min after TRH. Whether this observation is related to time, dose, or method of determination is not known.

The second purpose was to determine if the administration of TRH could be used as a test of pituitary reserve. This was confirmed. Three of five patients with craniopharyngiomas (group IV, Table II) did not release TSH after TRH administration. A positive response was observed, however, in two patients (T. H. and L. M.). T. H. had organic hypopituitarism with evidence for TSH deficiency (serum T4 concentration of 0.1 and FT4 concentration of 0.2 ng/100 ml). L. M. had an intrasellar craniopharyngioma which had not been operated upon, and had borderline thyroid function tests (serum T4 concentration of 3.8 μg/100 ml

and FT4 concentration of 1.2 ng/100 ml). Both patients had a deficiency of GH, ACTH, luteinizing hormone (LH), and follicular-stimulating hormone (FSH). Probably the pituitary was intact in these two patients but there was damage to the hypothalamus or hypothalamic vessels.

The third purpose of the study was to determine if some patients with idiopathic growth hormone deficiency plus thyrotropin deficiency responded normally to TRH with TSH release. Of the 13 patients who fell in this category, 10 did respond normally. This is indicative that these patients with idiopathic hypopituitarism are able to make TSH and are responsive to TRH, but are deficient in TRH supply to the pituitary. Three patients with idiopathic hypopituitarism (group III B) did not respond to TRH and one must conclude that these patients either have a primary defect in their pituitary gland or that their pituitary gland has become unresponsive to TRH from long-standing inactivity. All three of these patients were panhypopituitary patients and two (M. S. and W. B.) had exceedingly severe symptoms.

An additional purpose of the study was to correlate in patients with idiopathic hypopituitarism the responses to TRH, Piromen, and EP-AITT. Aarskog, Blizzard, and Migeon (17) and Raiti, Blizzard, Johanson, Davis, and Migeon (18) previously demonstrated in some of these patients that a normal cortisol response occurred when Piromen was given, although they had not responded normally to Metopirone. These data suggested at that time that the pituitary gland of these patients with apparent ACTH deficiency could release ACTH if the appropriate stimulus was given, and that the etiology of idiopathic hypopituitarism in some instances may not be a primary disease of the pituitary. In the current study, nine patients with idiopathic hypopituitarism who had an abnormal Metopirone test also received TRH. Eight (all in groupts II and III A) of these nine responded normally to both stimuli indicating the pituitary could release ACTH and TSH if appropriately stimulated. The ninth patient (M. S.) responded normally to Piromen with cortisol release but did not respond to TRH. This suggests that even M. S. in group III B might have a defect in releasing factor instead of in pituitary hormone production, and that with continued TRH stimulation she might have had TSH release.

Five of the patients who responded to TRH were given EP-AITT tests to determine if growth hormone would be released when a beta-adrenergic blocking agent (propranolol) was given. This agent augments the release of growth hormone in normal individuals (15). In no instance did any of these five patients release growth hormone, and therefore, no evidence could be obtained that the deficient growth hormone production in these patients could be altered with this stimulus. This does not exclude, however, the possibility that there is defective GHRH as a cause of the GH deficiency instead of defective production of GH.

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