Thyroid-Stimulating Hormone, Prolactin, and Growth Hormone Response to Thyrotropin-Releasing Hormone in Treated Children with Congenital Hypothyroidism

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ABSTRACT. The purpose of the present study was to assess thyroid-stimulating hormone (TSH), prolactin, and growth hormone responses to TRH stimulation in 12 congenitally hypothyroid children adequately treated with L-thyroxine from the first weeks of life. Although clinically euthyroid, six of these children were found to have abnormally high basal serum TSH concentrations despite clinical euthyroidism. Serum triiodothyroxine and L-thyroxine concentrations were normal and did not differ whether the children had elevated or normal basal serum TSH. All six of the children with high basal TSH had an exaggerated TSH response to TRH and 4 of them also had an augmented prolactin response to TRH. The children with normal basal TSH concentrations had normal TSH and prolactin responses to TRH. An abnormal ("paradoxical") elevation of growth hormone concentration in response to TRH was found in four of seven children in a separate group of patients who had prolonged, untreated primary hypothyroidism, but such responses were not found in any of the adequately treated children. These findings suggest the following conclusions: 1) the phenomenon of high serum concentrations of TSH in conjunction with normal L-thyroxine and triiodothyronine levels (and clinical euthyroidism), is prevalent in congenital hypothyroid patients. 2) These patients have an exaggerated response of their pituitary thyrotroph and lactotroph cells to TRH, presumably caused by selective and relative resistance of these cells to the inhibitory effects of thyroid hormones. 3) Congenital hypothyroidism is not associated with abnormal somatotroph cell responses to TRH. (*Pediatr Res* 19: 1037-1039, 1985)

Abbreviations

GH, growth hormone
PRL, prolactin
T3, triiodothyronine
T4, L-thyroxine
TRH, thyrotropin releasing hormone
TSH, thyroid stimulating hormone
CH, congenital hypothyroidism

In addition to elevated serum concentrations of TSH and an exaggerated response of TSH to TRH, other alterations in pitui-

tary regulation are well known in hypothyroid patients. Two examples of these alterations are the increased PRL response to TRH (1, 2) and the stimulation of GH secretion by TRH in hypothyroid children (3) and adults (4); these responses do not occur in normal subjects (5). It has been shown that many children suffering from congenital hypothyroidism manifest high serum TSH concentrations for prolonged periods despite adequate replacement therapy, clinical euthyroidism, and normal serum levels of thyroid hormones (7-10). It was suggested that this is due to an elevated threshold for thyrotroph cell TSH suppression by thyroid hormones. The purpose of the present study was to examine both the pituitary-thyroid negative feedback relationship and lactotroph and somatotroph regulation in children with congenital hypothyroidism.

MATERIALS AND METHODS

TRH tests were performed in 19 children. Group A consisted of 12 congenitally hypothyroid patients aged 1.6 to 9.3 yr attending our clinic for congenital hypothyroidism. All were diagnosed by neonatal thyroid screening during the first weeks of life, and all were treated from the time of diagnosis with T4 and followed by one of us (J.S.). Serum T4 levels were normalized in all children from the first month of treatment, and normal growth and development were observed. All group A children were clinically euthyroid for several months before the TRH test and had normal serum levels of thyroid hormones. Group B consisted of seven children, six girls, and one boy, aged 9 to 15.5 yr with primary acquired hypothyroidism present for at least several months prior to the time of evaluation and initiation of thyroid hormone treatment.

All tests were performed after informed consent of the parents. The TRH stimulation test was performed between 0900 and 1200 h, and the children were supine during the test. A short plastic catheter was inserted into an antecubital vein and normal saline solution was infused to maintain patency. Blood samples were obtained from the catheter upon insertion and every 15 to 30 min thereafter for 75 min. Fifteen minutes after insertion of the catheter (time 0), 7 µg/kg body weight TRH (Hoechst) was injected intravenously.

Blood samples were centrifuged within 1 h of sampling, and plasma was immediately frozen at -20° C until assayed. All serum samples were measured in duplicate in the same assay. GH was measured using the radioimmunoassay kit supplied by Sero Laboratories (Milan, Italy); lower limit of detection was 0.2 ng/ml. Serum PRL was measured by radioimmunoassay using materials kindly supplied by NIH, NIADDK, Bethesda, MD; normal values less than 20 ng/ml. Serum T4 (5 to 12 µg/dl), T3 (120 to 220 ng/dl), and TSH (normal values less than 6 µU/ml) were measured using radioimmunoassay kits supplied by Diagnostic Products Corp. (Los Angeles, CA).

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Table 1. TSH, PRL, and GH responses to intravenous TRH in group A1 children

No.	Sex	Age (yr)	T4 (0') (μg/dl)	T3 (0') (ng/dl)	TSH (μU/ml)				PRL (ng/ml)				GH (ng/ml)			
					0'	15'	30'	60'	0'	15'	30'	60'	0'	15'	30'	60'
1	F	5.75	9	273	3.2	20	18.5	13	22	39	31	20	0.9	0.7	0.45	0.3
2	F	9.33	13	144	3.2	27	23	17.5	11	38	34	20	0.3	1.3	1	1.2
3	F	5.33	9.5	115	2.1	15	13	7	31	39	33	28	1.7	0.8	0.3	0.3
4	M	3.25	12.1	207	1	13.5	14	5.6					1.6	2.3	1.4	1
5	F	6	12.2	167	4.1	16	19	19	11	32	23	19	3.2	1.0	0.4	0.3
6	M	3	18.3	140	1	7.2	8.6	5.3	10	45	38	31	0.5	1.0	0.5	0.5
Mean		5.44	12.35	174	2.4	16.5	16	11.2	17	39	32	24	1.4	1.2	0.7	0.6
± SEM		0.9	1.38	23	0.5	2.7	2.1	2.5	4	2	2.5	2.5	0.5	0.2	0.2	0.2

Table 2. TSH, PRL, and GH responses to intravenous TRH in group A2 children

No.	Sex	Age (yr)	T4 (0') (μg/dl)	T3 (0') (ng/dl)	TSH (μU/ml)				PRL (ng/ml)				GH (ng/ml)			
					0'	15'	30'	60'	0'	15'	30'	60'	0'	15'	30'	60'
7	M	2.2	11.1	178	34	82	108	77	2.5	20	20	11.5	1.9	1.5	1.2	1.0
8	M	5.2	10.3	150	28	101	114	64					6.3	3.1	1.0	0.3
9	M	3.75	13.5	148	29	50	180	49	27.5	145	120	68	1.3	1.3	0.9	1.2
10	F	4.7	13.9	183	28	60	200	132	29	140	107	61	3	2.5	2.3	1.2
11	F	1.7	11.2	146	11	35	129	60	9	59	50	34	2.2	3	2.8	1.8
12	M	2.2	12.3	191	16.5	42	49	51	31	156	131		1	0.9	1.1	0.6
Mean		3.2	12.05	166	24	62	130	72	20	104	86	44	2.6	2.1	1.6	1
± SEM		0.6	0.6	8.2	3.6	10.3	22	12.7	6	27	21	13	0.8	0.4	0.3	0.2

The normal plasma TSH concentration after 1 month of age is less than 6 μU/ml, and the normal TSH response to TRH is at least twice the basal concentration, but not exceeding 35 μU/ml [in agreement with previous reports (11)]. An abnormal ("paradoxical") plasma GH elevation after TRH injection was defined as at least twice the basal concentration (and above 5 ng/ml) as reported previously (3).

Statistical analyses were performed using Student's *t* test for paired and unpaired data. All values are recorded as mean and SEM.

RESULTS

The children in group A were divided into two subgroups, A1 and A2 (Table 1). A1 consisted of children with basal TSH concentrations below 5 μU/ml; children in group A2 had basal TSH levels greater than 10 μU/ml. The children of subgroup A2 were slightly younger than those of subgroup A1, but the age difference is not statistically significant (Table 2). The concentrations of T3 and T4 in each subgroup were close to the upper limit of the normal range. The mean concentrations of T3, T4, mean basal PRL, and GH did not differ statistically in the two subgroups (Fig. 1).

There was a marked difference in the TSH and PRL responses to TRH in the two subgroups. All children of subgroup A1 with normal basal TSH concentrations responded to TRH with a normal elevation of TSH (mean peak value at 15 min, 16.5 ± 2.7 μU/ml) and PRL (mean peak value at 15 min, 38.6 ± 2.7 ng/ml). The children of subgroup A2 responded to TRH with an exaggerated elevation of TSH (mean peak value at 30 min, 130 ± 22 μU/ml). Four of group A2 children also demonstrated an exaggerated PRL response (mean peak value of the entire subgroup at 15 min, 104 ± 27 ng/ml). There was no increase in serum GH concentrations in response to TRH in any of the 12 A group children.

The mean T4 and T3 concentrations in seven children with prolonged primary congenital hypothyroidism (group B) were very low (1.9 ± 0.4 and 67 ± 15 , respectively). The mean basal TSH levels were very high (mean 307 ± 93 μU/ml) with an exaggerated TSH response (48 to 1200 μU/ml), and both the

Table 3. The GH response to TRH in group B children

No.	Age (yr)	Sex	GH (ng/ml)			
			0'	15'	30'	60'
1	9.2	F	0.4	2.8	1.1	0.5
2	11	F	1.1	6.4	8	1.3
3	11.6	F	1.2	5.9	5.3	11.2
4	11.8	F	1.0	0.2	0.5	2.5
5	15.6	F	2.3	4.3	3.7	3.0
6	12	F	3.9	6.9	17.3	5.2
7	9.6	M	2.3	7.5	13	7.5
Mean	11.5		1.8	4.9	7.0	4.5
± SEM	0.8		0.4	1.0	2.4	1.4

mean basal TSH level and the TSH response to TRH were significantly greater than in subgroup A2 children ($p < 0.01$).

The mean basal PRL concentration in group B children was higher, but not significantly so, than in subgroups A1 and A2. The PRL response to TRH was exaggerated in group B (mean peak value at 30 min, 134 ± 69 ng/ml), similarly to the response in subgroup A2. Four of the 7 children of group B responded to TRH with an abnormal elevation of serum GH (Table 3).

DISCUSSION

In six of the 12 congenitally hypothyroid group A children who had been adequately treated with thyroxine from the first weeks of life (subgroup A2), a high basal serum TSH and exaggerated TSH and PRL responses to TRH were found. In these children T4 and T3 levels were in the upper normal range and were similar to values in the six subgroup A1 children with normal basal TSH and normal TRH-stimulated TSH and PRL responses. This phenomenon of high serum TSH concentrations despite clinical and biochemical euthyroidism (7–10) may be described as "selective relative resistance of the thyrotroph to the negative feedback effect of thyroid hormones" (12). It is "selective" because the peripheral tissues respond normally to thyroid hormones as reflected by clinical euthyroidism, and "relative"

Fig. 1. PRL responses to intravenous TRH in children of subgroup A1 (open circles), subgroup A2 (closed circles), and group B (triangles). The Group B values at 15, 30, and 60 min differ significantly from the A1 values ($p < 0.01$). The A2 values at 15 and 30 min also differ significantly from the A1 values (** $p < 0.01$).

because excessive TSH secretion can usually be suppressed when the child is made hyperthyroid with excessive doses of T4 (our unpublished data).

The present results show that resistance to the negative feedback effects of thyroid hormones in infants with congenital hypothyroidism, as reflected by exaggerated responses to exogenous TRH, is not limited to the thyrotroph cell, but also involves the lactotroph. In contrast, the somatotrophs responded normally in all group A children; the normal tendency of serum GH to decrease after TRH administration (3) was observed. Four of the seven children with prolonged, untreated, acquired, primary hypothyroidism (group B) responded with abnormal ("paradoxical") elevation in serum GH concentrations after TRH. This response has been reported previously in hypothyroid children (3) and adults (4). The cause for the paradoxical GH response in hypothyroidism is not known. It might be an expression of a regulatory reaction to the hyperactivity of the GH system characteristic of this state (14–16). According to this concept, restoring the GH pituitary reserve and normalizing the production of somatomedins abolishes the paradoxical response to TRH. In several reports it has been shown that the decline in pituitary GH concentration occurs only in severe prolonged hypothyroidism and that even suboptimal replacement of thyroid hormones rapidly restores GH concentration in the rat (15, 17). In any case, the subtle regulatory changes causing exaggerated TSH and PRL responses to TRH are independent of this GH response.

The pathophysiologic mechanism(s) causing the resistance of pituitary thyrotrophs and lactotrophs to the inhibitory effect of thyroid hormones is not clear. Hypothyroidism affects both the hypothalamus and the pituitary causing alteration in the structure (18, 19) and function (20–22) of several pituitary cells, as

well as alterations in secretion of selected hypothalamic regulatory peptides (23) in laboratory animals. It is suggested that in cases of congenital hypothyroidism some of these changes may persist despite adequate replacement therapy; in such infants there might have been an abnormal maturation of the hypothalamic-pituitary axis in a hypothyroid milieu.

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