

Human prolactin and thyrotropin concentrations in the serums of normal and hypopituitary children before and after the administration of synthetic thyrotropin-releasing hormone

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Research Article

Synthetic thyrotropin-releasing hormone (TRH) was administered to normal children and hypopituitary patients in a dose of 7 µg/kg i.v. over 30-60 sec. Serum thyrotropin (TSH) and prolactin (HPr) concentrations were measured by radioimmunoassay before and at 15-min intervals for 2 hr after TRH. In 20 normal children HPr rose from a mean baseline value of 7.0 ± 1.2 (SEM) ng/ml to a mean peak value of 39.5 ± 5 ng/ml.

In 11 patients with growth hormone (GH) deficiency without TSH deficiency. HPr values rose from a mean baseline of 3.6 ± 0.8 ng/ml to a mean peak value of 13.9 ± 2.8 , a significantly less peak response as compared with normal children ($P < 0.005$). The TSH responses to TRH, however, were statistically indistinguishable from those of normal children.

In 10 patients with GH and TSH deficiency both the mean baseline HPr levels (25.0 ± 5 ng/ml) and the mean peak HPr levels after TRH (68.5 ± 10 ng/ml) were significantly higher ($P < 0.005$ and < 0.025) than those of normal children. Similar comparisons were also true for the peak TSH responses ($P < 0.05$). Two panhypopituitary patients released no TSH and only small amounts of HPr after TRH. After thyroid replacement therapy in eight of the patients with GH and TSH deficiency, the mean HPr baseline levels (7.6 ± 1.0 ng/ml) and peak levels (23.3 ± 4.6 ng/ml) after the same dose of TRH [...]

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Human Prolactin and Thyrotropin Concentrations in the Serums of Normal and Hypopituitary Children before and after the Administration of Synthetic Thyrotropin-Releasing Hormone

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ABSTRACT Synthetic thyrotropin-releasing hormone (TRH) was administered to normal children and hypopituitary patients in a dose of 7 $\mu\text{g}/\text{kg}$ i.v. over 30–60 sec. Serum thyrotropin (TSH) and prolactin (HPr) concentrations were measured by radioimmunoassay before and at 15-min intervals for 2 hr after TRH. In 20 normal children HPr rose from a mean baseline value of 7.0 ± 1.2 (SEM) ng/ml to a mean peak value of 39.5 ± 5 ng/ml.

In 11 patients with growth hormone (GH) deficiency without TSH deficiency, HPr values rose from a mean baseline of 3.6 ± 0.8 ng/ml to a mean peak value of 13.9 ± 2.8 , a significantly less peak response as compared with normal children ($P < 0.005$). The TSH responses to TRH, however, were statistically indistinguishable from those of normal children.

In 10 patients with GH and TSH deficiency both the mean baseline HPr levels (25.0 ± 5 ng/ml) and the mean peak HPr levels after TRH (68.5 ± 10 ng/ml) were significantly higher ($P < 0.005$ and < 0.025) than those of normal children. Similar comparisons were also true for the peak TSH responses ($P < 0.05$). Two panhypopituitary patients released no TSH and only small amounts of HPr after TRH. After thyroid replacement therapy in eight of the patients with GH and TSH deficiency, the mean HPr baseline levels

(7.6 ± 1.0 ng/ml) and peak levels (23.3 ± 4.6 ng/ml) after the same dose of TRH were significantly less than their pretreatment levels ($P < 0.001$ and < 0.01) and were within the range for normal children.

Synthetic TRH stimulates the simultaneous release of TSH and HPr in normal children and most hypopituitary patients. When the concentrations of thyroxine (T4) and triiodothyronine (T3) are low, the levels of HPr before and after TRH are elevated. After thyroid replacement therapy, HPr levels decrease to normal. T4 and/or T3 may condition the production or effects of prolactin-inhibiting factor (PIF) activity. The TSH and HPr responses after TRH in hypopituitary patients will determine whether the primary defect resides in the pituitary or hypothalamus, but cannot delineate the hypothalamic defect as a deficiency of hypothalamic hormone production or neurohumoral transmission.

INTRODUCTION

Thyrotropin-releasing hormone (TRH)¹ releases thyrotropin (TSH) in vivo from the pituitaries of normal adults (1–10) and children (11, 12), and most patients with idiopathic hypopituitarism (11–12). We have reported (11) that 13 of 13 children with growth hormone (GH) deficiency without apparent TSH deficiency, 10 of 13 children with idiopathic GH deficiency

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¹ Abbreviations used in this paper: GH, growth hormone; HPr, prolactin; PIF, prolactin-inhibiting factor; T3, triiodothyronine; T4, thyroxine; TSH, thyrotropin; TRH, thyrotropin-releasing hormone.

plus TSH deficiency, and 1 of 5 children with GH and TSH deficiency secondary to operative procedures for craniopharyngiomas released TSH to a comparable extent as normal children after TRH injection. The interpretation of these data by our group (11) and similar data by Costom, Grumbach, and Kaplan (12) was that at least some children with apparent TSH deficiency had idiopathic hypopituitarism because an apparently normal pituitary gland was not receiving the appropriate releasing stimulus for TSH.

Subsequent to the demonstration that TRH releases TSH from the pituitary, TRH has also been shown to elevate prolactin levels from cloned rat pituitary tumor cells in vitro (13) and in normal subjects (14-15). The current study was undertaken to evaluate the release of prolactin (HPr) secondary to TRH stimulation in normal children and in the hypopituitary patients referred to above.

METHODS

Unless otherwise designated in the tables, 7 μg of TRH per kg of body weight were given i.v. over a 30-60 sec period. Serum samples were collected at -20, 0, 15, 30, 45, and 60 min, and in most patients at 90 and 120 min. TSH, serum thyroxine, free thyroxine (T4) (16), and GH concentrations (17), and serum HPr concentrations (18, 19) were measured as previously reported. No cross-reaction between TSH, HPr, or GH could be demonstrated in the assay systems.

The majority of normal children were siblings of patients seen in our endocrine clinic and were prepubertal. One patient was seen for intrauterine growth retardation and two

children had recovered from psychosocial dwarfism. One child had a diagnosis of constitutional short stature after appropriate testing revealed no evidence of endocrine disease. These individuals without endocrine disease are designated as "group I." Children or young adults with failure of GH to be released secondary to a combined arginine-insulin tolerance test (19), but with normal serum thyroxine and free T4 determinations, are categorized as "group II." These patients have GH deficiency *without* apparent TSH deficiency. Since there is no readily available test for TSH reserve, it is possible that these individuals might have only a limited response of TSH secretion if it were possible to test for this. The patients in group III were children or young adults with GH deficiency plus evidence for TSH deficiency since the serum thyroxine and free T4 determinations were below the normal range. The function of other pituitary hormones in these same patients in groups II and III has been previously reported (11). All patients with TSH deficiency in group III had not been taking thyroid hormone therapy for at least 10 days before testing. All patients requiring steroid therapy were maintained on cortisone replacement in physiological doses. Net secretory responses of TSH and HPr were calculated by subtracting the mean basal level (-20 and 0 min) from the mean of the 15, 30, 45, and 60-min levels and multiplying by 15. The units of this calculated parameter are microunit-minutes or nanogram-minutes, respectively. For statistical computations, one-half of the lowest value for the sensitivity of the assay was used when a TSH or HPr concentration was below the sensitivity of the assay (11).

RESULTS

Normal children (Table I). The quantitative responses of HPr and TSH to TRH injections by individuals are given in Table I, and the group response is compared with that of other groups in Fig. 1. Fasting levels of HPr ranged from < 2.3 ng/ml to a maximum of 23.0 ng/ml. The majority of fasting HPr levels were less than 10 ng/ml and the average of the means at -20 and 0 min was 7.0 ± 1.2 ng/ml (SEM). The average of the mean TSH levels at these times was 2.2 ± 0.3 $\mu\text{U}/\text{ml}$. By 15 min after injection both TSH and HPr concentrations had increased significantly, and concentrations of both hormones had returned to or were returning to basal levels by 90 min postinjection. The mean HPr concentration peaked at 15 min and the mean TSH concentration at 30 min. However, the peak values for each hormone at 15 and 30 min were within 1 SEM, and suggests that both hormones are released simultaneously and promptly after the i.v. injection of TRH.

Group II: hypopituitary patients with GH deficiency without apparent TSH deficiency (Table II). As previously reported (11) and as demonstrated in Fig. 1, the TSH response of children in group II is statistically indistinguishable from that of normal children (group I). The mean peak response of TSH in group II was 21.0 ± 3.4 $\mu\text{U}/\text{ml}$, and is almost identical to the peak response in group I of 21.7 ± 3.1 $\mu\text{U}/\text{ml}$. HPr concentrations in individuals in group II, however, increased to

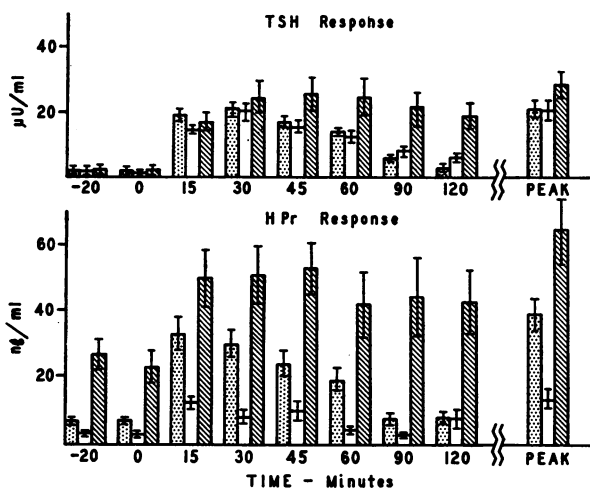


FIGURE 1 Thyrotropin and human prolactin concentrations before and after the injection of thyrotropin releasing hormone i.v. in normal children (group I, stippled bars), patients with growth hormone deficiency without apparent thyrotropin deficiency (group II, open bars), and patients with both growth hormone and thyrotropin deficiency (group III, cross-hatched bars). The vertical lines at the top of each bar represent one standard error of the mean (SEM).

TABLE I
Group I: Control Children

Name	Age	Sex	Diagnosis	TRH dose	Time, min											Peak response	Net Secretion response	T4/free T4
					-20	0	15	30	45	60	90	120						
1. H. S.	13.2	F	N	7.0	TSH* HP†	<1.5	10.4	7.7	8.9	8.4	6.5	8.9	8.4	6.5	8.9	95.6	4.1/1.7	
2. A. B.	12.1	M	N	7.0	TSH HP†	<1.5	7.0	13.0	15.6	11.8	10.8	15.6	11.8	10.8	15.6	109.5	4.4/1.4	
3. D. R.	5.9	M	Noonans	7.0	TSH HP†	3.0	2.4	26.8	26.5	20.4	14.3	26.5	20.4	14.3	26.8	289.5	5.3/2.6	
4. K. S.	7.9	F	N	7.0	TSH HP†	<1.5	31.4	30.3	31.4	27.8	22.0	31.4	27.8	22.0	31.4	395.5	5.4/1.7	
5. T. S.	4.7	F	N	7.0	TSH HP†	2.5	2.3	16.6	14.4	14.2	7.8	16.6	14.4	7.8	16.6	386.6	5.2/1.4	
6. J. J.	5.5	M	IUGR	7.0	TSH HP†	2.0	1.8	15.9	24.3	19.1	17.6	24.3	19.1	17.6	24.3	259.8	3.8/1.7	
7. B. Y.	6.7	F	PD	7.0	TSH HP†	<1.2	7.4	40.2	34.2	28.2	17.2	34.2	28.2	17.2	34.2	241.8	5.2/1.6	
8. J. Y.	8.7	F	PD	7.0	TSH HP†	<1.2	8.4	4.1	5.2	4.3	2.4	5.2	4.3	2.4	5.2	41.2	4.5/1.8	
9. S. N.	9.7	F	PD	7.0	TSH HP†	<1.2	3.4	26.6	43.6	47.4	18.4	43.6	47.4	18.4	47.4	279.3	5.2/2.0	
10. K. W.	4.8	M	SS	7.0	TSH HP†	2.8	2.9	12.2	9.6	7.8	7.8	9.6	7.8	7.8	12.2	417.0	5.5/2.5	
11. J. H.	11.11	F	N	7.0	TSH HP†	<1.5	11.2	56.0	29.0	25.6	20.2	29.0	25.6	20.2	29.0	330	4.3/1.7	
12. L. C.	13.0	F	N	7.0	TSH HP†	3.3	6.2	116.4	64.8	72.9	81.0	64.8	72.9	81.0	71.4	636.7	5.4/1.8	
13. S. P. U.	11.2	F	N	7.0	TSH HP†	<1.2	6.1	16.0	19.9	15.3	10.3	19.9	15.3	10.3	19.9	328.1	4.5/1.8	
14. M. A. U.	8.7	M	N	7.0	TSH HP†	1.9	3.2	18.9	19.6	17.3	17.3	19.6	17.3	17.3	19.6	250.5	5.5/2.0	
15. Marg. U.	7.2	F	N	7.0	TSH HP†	<1.2	7.8	29.7	28.7	21.0	16.6	28.7	21.0	16.6	29.7	164.7	4.4/1.6	
16. Mic. U.	7.2	F	N	7.0	TSH HP†	<1.2	6.4	13.5	8.4	6.4	5.8	8.4	6.4	5.8	11.5	101.7	6.0/2.5	
17. J. R.	12.5	M	N	7.0	TSH HP†	7.2	5.6	29.4	32.6	30.9	24.0	32.6	30.9	24.0	32.6	48.5	3.8/1.4	
18. C. R. U.	8.7	M	N	7.0	TSH HP†	<1.2	4.2	9.7	13.3	11.2	10.0	13.3	11.2	10.0	13.3	147	4.7/1.7	
19. S. M.	9.9	F	N	7.0	TSH HP†	9.8	13.0	54.4	43.2	40.4	18.2	43.2	40.4	18.2	54.4	438.3	4.5/1.8	
20. C. M.	12.0	F	N	2.6	TSH HP†	<1.5	3.8	40.4	19.9	17.3	15.9	19.9	17.3	15.9	19.9	238.0	3.9/1.6	
					TSH	2.4±0.4	2.0±0.3	19.7±2.0	21.5±2.0	17.7±1.7	14.6±1.2	21.5±2.0	17.7±1.7	14.6±1.2	21.7±3.1	251±25	4.7±0.6	
					HP†	7.1±1.2	6.9±1.2	33.0±5	29.8±4.0	24.1±4.0	18.8±3.5	29.8±4.0	24.1±4.0	18.8±3.5	29.5±5.0	331±65	1.8±0.3	

* Microunits per milliliter.
 † Nanograms per milliliter.
 § Not used in calculations. IUGR, intrauterine growth retardation; PD, psychosocial dwarfism; SS, constitutional short stature.
 || Mean ±SEM.

TABLE II
Group II: Growth Hormone-Deficient Children

	Name	Age	Sex	TRH dose	Time, min										Peak response	Net secretion response	T4/free T4
					-20	0	15	30	45	60	90	120					
1.	J. P.	19.7	M	7.0	TSH 3.5 HPr 3.5	1.9 <1.4	28.0 9.5	45.0 7.6	26.5 6.2	24.3 7.9	20.2 5.4	11.8 1.7	45.0 9.5	423.7 79.5	4.5/1.6		
2.	G. S.	12.5	M	7.0	TSH <1.2 HPr 6.9	<1.2 <1.4	7.1 7.2	9.8 <1.4	7.3 6.7	6.2 2.5	3.1 <1.4	1.6 2.0	9.8 7.2	95.3 5.4	5.2/2.0		
3.	C. B.	3.5	M	7.0	TSH <1.2 HPr 5.4	<1.2 5.0	16.5 15.3	18.4 7.0	16.0 17.2	6.9 6.0	4.2 2.7	2.0 2.7	18.4 17.2	198.0 92.7	4.8/2.5		
4.	L. L.	14.7	M	7.0	TSH <1.2 HPr 7.7	<1.2 <1.4	12.3 10.9	16.7 4.9	19.0 8.4	16.8 5.3	15.6 2.2	11.9 <1.4	19.0 10.9	224.2 41.7	3.5/1.2		
5.	S. B.	7.9	M	7.0	TSH 1.5 HPr <1.4	1.7 <1.4	9.3 <1.4	11.5 2.4	8.5 <1.4	4.6 <1.4	5.3 <1.4	3.3 <1.4	11.5 2.4	103.1 3.8	4.8/2.0		
6.	B. S.	16.5	M	7.0	TSH <1.2 HPr 2.0	<1.2 8.5	8.1 23.6	9.8 16.5	8.9 31.6	7.1 9.7	3.9 3.2	2.4 15.7	9.8 31.6	108.3 225.8	5.0/1.5		
7.	F. M.	7.5	M	6.1	TSH 3.9 HPr 1.4	3.0 <1.4	16.9 5.8	15.8 3.0	13.7 5.1	11.2 <1.4	11.2 <1.4	16.9 5.8	164.2 36.5	4.3/1.7			
8.	C. B.	15.5	M	7.0	TSH 4.3 HPr 8.8	<1.2 9.2	15.3 9.3	18.0 2.6	12.5 6.7	9.8 1.7	6.0 1.9	3.6 18.3	18.0 18.3	167.0 -58.8	4.8/1.7		
9.	C. S.	15.6	M	7.0	TSH 3.3 HPr <1.4	2.8 <1.4	20.2 9.7	26.5 5.0	21.4 1.4	19.4 8.0	3.9 2.0	10.9 <1.4	26.5 9.7	282.3 69.5	3.9/1.7		
10.	R. B.	17.9	M	7.0	TSH 2.3 HPr 3.1	1.6 3.8	23.0 28.0	27.6 28.0	21.3 22.4	18.0 2.4	7.3 6.6	7.3 28.4	27.6 28.4	307.8 250.5	4.4/1.6		
11.	T. L.	15.5	M	7.0	TSH <1.2 HPr <1.4	<1.2 <1.4	10.1 11.6	10.7 7.9	8.0 3.3	7.9 2.6	4.1 3.1	2.0 2.2	10.7 11.6	118.8 84.3	3.9/1.7		
12.*	S. C.	10.0	F	7.0	TSH 2.2 HPr 126	<1.5 110	16.9 106	17.3 205	13.1 75.8	12.3 159	8.9 83	6.6 129	17.3 159.0	192.0 276.8	4.9/1.9		
					TSH† 2.3±0.3 HPr† 3.9±0.7	1.8±0.2 3.3±0.8	15.2±1.8 12.0±1.9	20.6±3.0 7.8±2.0	16.0±1.9 10.0±2.8	13.1±2.1 4.4±1.0	8.3±1.8 3.0±0.5	6.3±1.4 7.5±3.1	21.0±3.4 13.9±2.8	217±36 65.0±61.5	4.5±0.5 1.7±0.1		

* Not included in tabulation.
† Mean ±SEM.

TABLE III-A
Group III: GH + TSH-Deficient Children

Name	Age	Sex	TRH dose	Time, min							Peak response	Net secretion response	T ₄ /free T ₄
				-20	0	15	30	45	60	90			
1. J. Mc.	10.2	M	7.0 TSH HP†	3.0 49.2	1.7 64.8	17.0 44.6	24.6 50.6	30.9 37.2	27.5 57.8	33.8 33.8	34.6 28.8	339.7 -141.8	2.5/1.0
2. H. S.	17.7	M	7.0 TSH HP†	5.0 28.2	5.3 17.4	40.0 21.8	48.8 31.0	40.5 53.4	33.3 7.7	25.1 11.8	16.9 12.1	532.5 85.2	2.2/0.9
3. W. E.	27.5	M	7.0 TSH HP†	3.8 11.7	4.6 12.8	32.6 31.2	54.0 30.6	59.2 61.4	61.3 47.8	55.7 33.8	47.1 33.4	713.5 456.8	2.3/0.8
4. M. Mc.	12.0	M	7.0 TSH HP†	2.0 6.1	2.1 8.4	29.5 36.4	30.3 28.2	26.1 12.4	22.9 10.7	4.3 6.9	10.7 4.9	378.0 221.0	2.9/1.0
5. L. B.	7.9	M	7.0 TSH HP†	4.2 20.6	4.4 11.3	28.4 62.4	40.4 111.2	44.1 64.6	41.3 42.4	21.7 26.2	21.7 31.6	513.7 811.5	2.6/1.0
6. P. H.	16.4	M	7.0 TSH HP†	<1.2 19.7	<1.2 21.0	6.9 41.0	14.4 38.0	16.8 44.4	18.0 28.2	20.4 26.2	21.7 44.4	191.6 262.5	2.9/0.8
7. D. B.	18.0	M	7.0 TSH HP†	<1.2 47.0	<1.2 39.2	3.9 129.0	9.6 104.0	7.8 120.0	8.1 135.0	6.6 152.0	2.6 123.0	91.5 754.7	0.9/0.6
8. E. T.	8.9	M	7.0 TSH HP†	<1.2 19.3	2.7 23.8	7.5 62.2	13.3 48.8	16.3 47.6	18.0 31.2	21.3 31.2	17.8 39.4	177.0 389.3	2.1/0.9
9. D. R.	27.4	M	7.0 TSH HP†	1.6 63.0	<1.2 38.4	18.4 81.6	26.0 55.4	36.3 87.2	38.8 80.0	34.5 81.5	25.5 83.2	426.7 380.3	1.6/0.6
10. M. H.	11.9	F	7.0 TSH HP†	3.4 6.4	2.5 4.0	6.6 18.0	8.8 28.6	9.0 21.6	9.5 6.5	9.5 28.6	9.5 28.6	82.8 202.2	3.6/1.0
11. M. L.	21.4	M	7.0 TSH HP†	<1.2 23.4	<1.2 13.9	2.2 24.4	2.8 35.8	1.9 30.2	1.6 14.7	<1.2 23.6	<1.2 30.6	13.1 113.7	0.3/0.2
12.* Do. B.	22.9	F	7.0 TSH HP†	<1.2 320	<1.2 400	6.9 720	14.4 462	16.8 376	18.0 438	20.4 356	21.7 324	191.5 2085.0	2.9/0.8
13.* W. B.	23.4	M	7.0 TSH HP†	<1.2 5.6	<1.2 9.1	<1.2 3.6	<1.2 11.0	<1.2 7.7	<1.2 6.5	<1.2 10.1	<1.2 5.4	<1.2 11.0	0.2/0.2
14.* M. S.	13.0	F	7.0 TSH HP†	<1.2 8.5	<1.2 8.2	<1.2 2.4	<1.2 4.8	<1.2 15.2	<1.2 6.1	<1.2 6.3	<1.2 3.9	<1.2 -17.5	1.4/0.6
			TSH†	2.5±0.3	2.5±0.4	17.5±3.5	24.8±5.0	25.8±5.0	25.5±5.0	22.5±5.0	19.8±4.0	315±60	2.17±0.89
			HP†	26.8±5.0	23.2±5.0	50.2±9.0	51.1±8.1	52.7±8.2	42.0±10.0	44.5±12.0	43.0±10.0	321±67	0.83±0.29

* Not used in calculations.
† Mean ±SEM.

TABLE III-B
Group III: Prolactin* Responses before and after Thyroid Therapy

Name	Thyroid therapy	Time, min						Peak response	Net secretory response	
		-20	0	15	30	45	60			
2.	H. S.	before	28.2	17.4	21.8	31.0	53.4	7.7	53.4	85.2
		after	8.4	11.0	20.0	26.0	9.6	15.5	26.0	121.5
3.	W. E.	before	11.7	12.8	31.2	30.6	61.4	47.8	61.4	456.8
		after	9.0	7.2	24.5	17.5	13.0	15.5	24.5	142.5
4.	M. Mc.	before	6.1	8.4	36.4	28.2	12.4	10.7	36.4	221.0
		after	10.5	7.7	21.0	17.5	9.2	8.4	21.0	73.5
5.	L. B.	before	20.6	11.3	62.4	111.2	64.6	42.4	111.2	811.5
		after	3.8	10.0	17.0	18.0	22.0	—	22.0	—
6.	P. H.	before	19.7	21.0	41.0	38.0	44.4	28.2	44.4	262.5
		after	4.9	5.6	13.0	22.5	18.0	16.0	22.5	181.9
7.	D. B.	before	47.0	39.2	129.0	104.0	120.0	135.0	152.0	754.7
		after	11.0	18.0	51.0	51.0	33.0	32.0	51.0	408.8
8.	E. T.	before	19.3	23.8	62.2	48.8	47.6	31.2	48.8	389.3
		after	5.2	4.7	11.5	13.0	8.6	6.0	13.0	72.4
11.	M. L.	before	23.4	13.9	24.4	35.8	30.2	14.7	35.8	113.7
		after	<2.8	3.8	6.0	5.8	4.2	3.3	6.0	33.0
12.	D. B.	before	320.0	400.0	720.0	462.0	376.0	438.0	720.0	2085.0
		after	200.0	187.0	236.0	180.0	204.0	218.0	236.0	240.0

* Expressed in nanograms per milliliter.

a lesser extent than those of normal children (13.9 ± 2.8 ng/ml vs. 39.5 ± 5 ng/ml in group I). The mean peak responses of groups I and II were significantly different ($P < 0.005$). The net secretory responses also were different ($P < 0.005$). One patient (S. C.) who was clinically indistinguishable from all other group II patients nonetheless was obviously different, as she had very high levels of HPr before and throughout the test. The data obtained in this patient were not used to calculate the means of HPr and TSH since these results are opposite to the HPr responses of the remainder of the group. Although not presented in the table, the HPr and TSH responses in one patient (F. M.) were statistically similar when doses of 1.0 and 6.1 μ g of TRH per kg of body weight were administered. We found similar responses in one patient (T. L.) when TRH was administered for 30 min and 60 sec.

Group III: hypopituitary patients with GH deficiency and TSH deficiency (Table III-A). The first 10 patients of the 14 listed in Table III differ from the last four. W. B. and M. S. were the most severely affected patients with idiopathic hypopituitarism we have observed. They did not release measurable amounts of TSH and released only small amounts of HPr after TRH stimulation. M. L. released very small amounts of TSH but normal amounts of HPr. D. B. released amounts of TSH comparable to normals but had extremely elevated HPr levels with a massive absolute increment after TRH. Because the last three patients

in Table III are obviously different than the others in respect to HPr, the data of these three were not used to calculate the mean values at each time for reasons cited above for patient S. C.

The mean HPr levels for -20 and 0 min (25.0 ± 5.0 ng/ml) were significantly higher ($P < 0.005$) than the mean baseline levels for normal children (7.1 ± 1.2 ng/ml). Similarly the peak responses of HPr (65.8 ± 10.0 ng/ml) were significantly higher ($P < 0.025$) than those of normal children (39.5 ± 5.0 ng/ml) as were the peak responses of TSH ($P < 0.05$).

Of the 14 patients in group III, nine had repeat TRH tests with the same amount of TRH after they had received replacement thyroid therapy for several months (Table III-B). In eight, the previously elevated mean baseline HPr levels were significantly lower ($P < 0.001$) after thyroid replacement therapy (7.6 ± 1.0 ng/ml), and were the same as group I. In addition, the peak HPr levels were significantly less ($P < 0.01$) after thyroid replacement therapy (23.3 ± 4.6 ng/ml) when compared with the levels while receiving no thyroid therapy. In the one remaining patient in group III who received the two TRH tests (Do. B.), her very high HPr levels fell to about half.

DISCUSSION

The explanation of why TRH stimulates HPr in addition to TSH in normal adults and children remains obscure. Jacobs et al. (14, 18) have adequately demon-

strated that the increased concentrations of HPr are real and not attributable to erroneous measurement of TSH or GH. GH did not increase after TRH in those patients in whom it was tested. This observation further indicates that TRH does not stimulate GH release and that GH and HPr do not cross-react in each assay system. HPr was significantly elevated in the pre-TRH samples in nine of the patients in Group III, and markedly increased in this group after TRH as compared with those in groups I and II. Since the patients in group III differed from those in group II primarily in that they had TSH deficiency in addition to GH deficiency, nine of the group III patients received the same dose of TRH after they had been on replacement thyroid therapy. The baseline levels and peak HPr responses to TRH had returned to normal in eight of the nine patients. One can logically deduce that T4 and/or triiodothyronine (T3) may have some inhibitory effect on the release of HPr, or be required for the synthesis or release of prolactin-inhibiting factor (PIF). Alternatively, TRH deficiency may be associated with PIF deficiency. Some of these patients (e.g., P. H. and D. B.) had normal metopirone stimulation tests and were sexually developed (11) suggesting that the HPr levels were not related to diminished steroid production. In a 7 yr old male with primary hypothyroidism we have found elevated fasting levels of 63.4 and 45.2 ng/ml of HPr, which rose excessively after TRH to 124 ng/ml. Thyroid replacement therapy in seven adult patients with primary hypothyroidism lowered basal HPr levels and blunted HPr responses to TRH (20). Although such data are not yet available in children, one may conclude that T4 and/or T3 block HPr release after TRH.

The elevation of HPr in the majority of patients in group III is indicative that most patients with idiopathic GH and TSH deficiency have increased secretion of HPr, presumably conditioned by T4 and/or T3 deficiency. It is equally possible that the hypothalamic defect that is responsible for GH and TSH deficiency when both occur could cause excessive HPr secretion through the abolition of PIF activity. Two patients (M. S. and W. B.) had minimal increases in both TSH and HPr after TRH suggesting that these two patients had primary pituitary disease instead of hypothalamic or releasing factor disease. Of the 11 patients in this group with normal TSH responses, indicating a hypothalamic etiology of their hypothyroidism, eight had elevated basal HPr levels. This suggests that the finding of elevation in fasting HPr in a patient with evidence of hypopituitarism should suggest the probability that the hypothalamus is at fault.

The explanation for the subnormal elevation of HPr by the majority of patients in group II when they

received TRH is an enigma. Although our group II patients are predominately prepubertal males, we did not find any statistical difference between the baseline levels or peak responses of HPr to TRH between males and females in group I. Statistically significant increase in the HPr response to TRH in women compared with men has been reported in adults (15, 20), and is probably secondary to the differences in circulating estrogen levels (15). This speculation would support our finding of no male-female differences in prepubertal children. None of these patients had received GH on the day TRH was given, and possibly GH is necessary for TRH to stimulate the release of HPr in the presence of PIF, but this hypothesis requires further testing before being accepted or rejected. Alternatively, these patients do appear to have intrinsic pituitary disease affecting both somatotrophs and lactotrophs. These cells produce structurally and functionally related hormones.

The testing for remaining pituitary tissue after hypophysectomy can be accomplished by administering TRH and observing HPr concentrations. However, the presence of antibodies to GH, HPr, and vasopressin in the sera of patients who have received therapy for diabetes insipidus with injections of pitressin tannate in oil must be recognized since cross-reactivity in the immunoassay will falsely elevate results (21).²

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