CLINICAL OBSERVATIONS ON THERAPEUTIC APPLICATIONS OF THYROTROPIN-RELEASING HORMONE (TRH)

SAKODA, Masahiro

(Citation)
The Kobe journal of the medical sciences,20(2):65-81

(Issue Date)
1974-06

(Resource Type)
departmental bulletin paper

(Version)
Version of Record

(URL)
https://hdl.handle.net/20.500.14094/0100488969

Kobe J. Med. Sci. 20, 65-81 June 1974

CLINICAL OBSERVATIONS ON THERAPEUTIC APPLICATIONS OF THYROTROPIN-RELEASING HORMONE (TRH)

Masahiro SAKODA, Takaaki KUSAKA, Hidetaro MORI, Makoto TATEIWA, Akihisa YAMADA, Masabumi UTSUMI, Fumikazu IGA, Hiroyuki MAKIMURA and Shigeaki BABA

Department of Internal Medicine, Division II Kobe University School of Medicine, Kobe, Japan

Indexing Words

thyrotropin-releasing hormone (TRH); thyrotropin (TSH); hypothyroidism

Masahiro SAKODA, Takaaki KUSAKA, Hidetaro MORI, Makoto TATEIWA, Akihisa YAMADA, Masabumi UTSUMI, Fumikazu IGA, Hiroyuki MAKIMURA and Shigeaki BABA. *Clinical Observations on Therapeutic Application of Thyrotropin-Releasing Hormone (TRH)*. Kobe J. Med. Sci. 20, 65-81, June 1974——An attempt was made to evaluate the possibility of therapeutic use of TRH in cases of hypothyrotropic hypothyroidism with special reference to its effects on pituitary-thyroid function. Firstly, changes in plasma TSH, serum T_4, serum PBI and T_3 RSU were observed in healthy volunteers who were treated with single or repeated oral administration of TRH.

Plasma TSH increase was obtained from 2 to 4 hours after the single oral administration of 4, 5 and 10 mg of TRH. Serum T_4 and PBI levels also rose 6-8 hours after single oral administration in doses of 3 mg and more. As to repeated administration, TRH was administered orally by 2 to 8 times in doses of 2, 4 and 6 mg, and observation continued 2 to 4 days. Almost all cases showed plasma TSH increase at 2 to 4 hours after each oral administration of TRH. Serum T_4, PBI and T_3 RSU also increased at 6 to 8 hours after each TRH administration. However, there was individual variation of TRH induced TSH increase and thyroid hormone response. Moreover, TRH administration was performed to 3 patients with hypothyroidism due to craniopharyngioma, ectopic pinealoma and suspected hypopituitarism. Both cases of craniopharyngioma and ectopic pinealoma showed sufficient pituitary TSH reserve to TRH test, in which plasma TSH, rising from low basal level, reached the normal range. Thus both cases may be postulated as belonging to the category of the so called hypothalamic hypothyroidism. The case of suspected hypopituitarism who has subclinical hypothyroidism, showed almost normal TSH increase to TRH test. Four mg of TRH was administered daily to these 3 patients for 3 weeks or more. Gradual increases of serum T_4, T_3 and PBI were obtained

Received for publication May 14, 1974

Authors' names in Japanese: 佐古田雅弘, 日下孝明, 森顕太郎, 立岩 真, 山田晃久, 内海正文 伊賢文計, 槙村博之, 馬場茂明

and these increases reached their peaks 2 weeks after the onset of the oral administration. Although one case showed the decrease of blood thyroid hormone concentration after the withdrawal of TRH administration, another case showed a continued high level of serum T_4, the level being within normal range even 2 and 6 weeks after the withdrawal. Further studies on therapeutic application of TRH would be significant for the development of replacement therapy on hypothyrotropic hypothyroidism.

INTRODUCTION

It has been well documented that synthetic thyrotropin-releasing hormone (TRH) plays an essential role in the regulation of pituitary TSH secretion in animals and in man. The recent availability of synthetic TRH makes it possible clinically studying on the effects of synthetic TRH in healthy subjects and in patients with hypothalamo-pituitary disorders. The results indicate that TRH might be utilized through enteral or parenteral routes as a pituitary TSH reserve test. Also, these observations have revealed the clinical entity of hypothalamic hypothyroidism, a new clinical entity, whose hypothyroidism is caused from hypothyrotropinism due to hypothalamic lesion.[12, 16, 18] Now, TRH is thought to be useful in therapeutic as well as in diagnostic applications because TRH has a specific thyrotropin-releasing activity from the anterior pituitary gland.

An attempt was made to evaluate the possibility of therapeutic application of TRH in healthy subjects and in patients with hypothyrotropic hypothyroidism with special reference to its effect on pituitary thyroid function.

MATERIALS AND METHODS

Thyrotropin-Releasing Hormone (TRH)

Thyrotropin-releasing hormone used in this study was synthesized following the method of Gillessen et al. [3] with slight modification. It was presented as pyroglutamyl-histidil-proline-amide in the form of acetate salt. TRH activity of this preparation was determined with *in vivo* and *in vitro* methods. Acute toxicity was tested in mice and subacute toxicity was examined in rats by intraperitoneal injection of synthetic TRH for 30 days before initiating this study.[14, 15] Each tablet for oral administration contains 1 mg of TRH.

Determination of plasma TSH and serum thyroid hormone concentration

Plasma TSH concentrations were measured by means of radioimmunoassay using the double antibody technique. Purified human TSH preparation for labelling with radioactive iodine and antiserum to TSH were supplied by the National Institute of Health Endocrinology Study Section. The Human Thyrotropin Research Standard A was used as standard. TSH was labelled with ^{125}I by the method of Greenwood et al. [4] Assay was performed by a modification of the method which was previously reported.[13] The minimal detectable concentration of plasma

TSH was 1.7 μU/ml in our laboratory. The serum PBI was measured by the autoanalyzer technique. An estimation of serum thyroid hormone concentration was performed with T_3 resin sponge uptake (T_3 RSU) and T_4 resin sponge uptake (T_4 RSU) which was measured by competitive binding, using commercially available kits. (Dainabot R-I. Lab., Ltd.)

Clinical subjects

Synthetic TRH was administered to 31 volunteers. The first 28 including one of the authors were healthy volunteers who had no clinical or laboratorical evidence of endocrine disorder. Subsequent volunteers were informed of the purpose of this study and of the experience of those who had received synthetic TRH. Verbal permission to perform these studies was obtained from the volunteers or their families by Dr. Sakoda. In addition to healthy subjects, TRH was given to 3 patients with hypothyrotropic hypothyroidism including each one case of ectopic pinealoma, craniopharyngioma and suspected hypopituitarism.

Both cases of ectopic pinealoma and craniopharyngioma were determined by means of histological examination after craniotomy.

TRH administration

Single oral administration of TRH was performed at 9 A.M. in doses of 1, 2, 3, 4, 5 and 10 mg. Effects of repeated oral administration were observed both in healthy volunteers and in patients with hypothyrotropic hypothyroidism. TRH in doses of 3 and 4 mg was orally administered for from 2 to 7 weeks to patients with hypothyrotropic hypothyroidism.

RESULTS

1. Effects of single oral administration of TRH in normal subjects (Table 1)

Single oral administration of TRH in doses of 1, 2 and 3 mg was not always effective on plasma TSH level; Certain subjects showed slight TSH increase while the other did not respond at all. Single oral TRH administration in doses of 4, 5 and 10 mg stimulated a rise in plasma TSH level in all normal subjects. A detectable TSH rise was observed within 1 hour and further rise followed over next 3 hours. Peak level of plasma TSH occurred at 4 hours after TRH administration with gradual fall over next 4 hours. The cases given higher doses of TRH showed the longer duration of increased TSH levels, however, individual variation of plasma TSH increase was observed in cases treated with 4, 5 and 10 mg of TRH. Serum T_4, PBI and T_3 RUS also rose 3 hours after oral TRH administration in doses of 3 mg and more, and this increase durated for at least 5 hours, while administration of 1 and 2 mg did not show any consistent effects on serum T_4, PBI and T_3 levels.

2. Effects of repeated oral administration of TRH in normal subjects

Six mg of TRH was administered daily to 3 male volunteers for 2 days and changes in plasma TSH, serum T_4, PBI, T_3RSU were estimated at 2, 4 and 8

Table 1 Effect of single oral administration of TRH on plasma TSH, serum T_4 and serum PBI.

Dose of TRH	Age	Sex	Plasma TSH (μU/ml) after TRH										Serum T_4 (μg/dl)							Serum PBI (μg/dl)				
			0	30′	1	2	3	4	6	8	12	24h	0	2	4	6	8	12	24h	0	2	4	6	8h
1mg	22	F	3.0	2.6	2.0	2.0		2.3	2.3	2.7		2.6												
1	28	M	2.0	1.7	1.7	3.3		1.7	2.4			1.7												
1	36	M	1.7	1.7	1.7	1.7		1.7	1.7	1.7		1.7												
2	22	F	2.0			5.3		4.3	2.3	2.6		1.7												
2	23	F	1.7			1.7		3.0	1.7	1.7		1.7												
2	40	M	1.7			1.7		1.7	1.7	1.7			9.5	9.4		8.5	8.7			6.3	6.2		5.6	5.6
3	29	M	1.7			1.7		1.7	1.7	1.7			10.5	12.5		11.3	12.0			6.9	8.2	9.8	7.3	7.9
3	29	M	1.7			5.0		1.7	1.7	1.7			13.0	13.6	15.0	18.0	16.0			8.5	8.9		11.9	10.5
4	22	F	1.7	1.7	1.7	5.4		8.6	5.0	2.0		2.3												
4	29	M	1.7			8.7			3.3	2.3			11.0	10.5		12.3	14.2			7.2	6.9		8.0	9.3
4	36	F	1.7			5.3					1.7		12.8	11.7				14.0						
4	29	M	1.7						4.29			1.7	13.4			15.6								
5	29	M	3.0	1.7	18.2	19.8	19.5	22.4	12.5	19.5		5.9	9.7	9.2	10.2	10.3	11.3		10.6					
5	24	F	1.7		12.9	13.3		18.8	14.1	6.5														
10	38	M	2.0	2.0	13.8	13.5	12.9	15.8	5.6	2.0		1.7	7.0	7.6	8.7	9.2	9.9		7.9					
10	26	M	1.7		21.0	23.6		27.8	26.5	17.8		4.9												
4	38	F											9.6	9.8		12.5	13.2			6.1	6.1		7.2	8.0
4	40	M											12.4	12.4	13.2									

hours after each adminstiration of TRH. Plasma TSH increased clearly 2-4 hours after each TRH administration and serum T_4, and PBI levels also rose 6-8 hours after TRH administration ; a rising pattern was similar to that of plasma TSH with 2-4 hours delay. Blood TSH and thyroid hormone concentrations returned to resting level 24 hours after TRH administration (Fig. 1). Four male volunteers were treated daily with 4 mg of TRH for 3 or 4 days. Case 2 (F.I.) and case 4 (H.M.) showed plasma TSH rise in early phase (2-4 hours after TRH administration) and blood thyroid hormone increase in later phase (4-8 hours after TRH administration) with gradual return to basal level over next 10-16 hours.

The time-response relationship was similar to that obtained from 6 mg

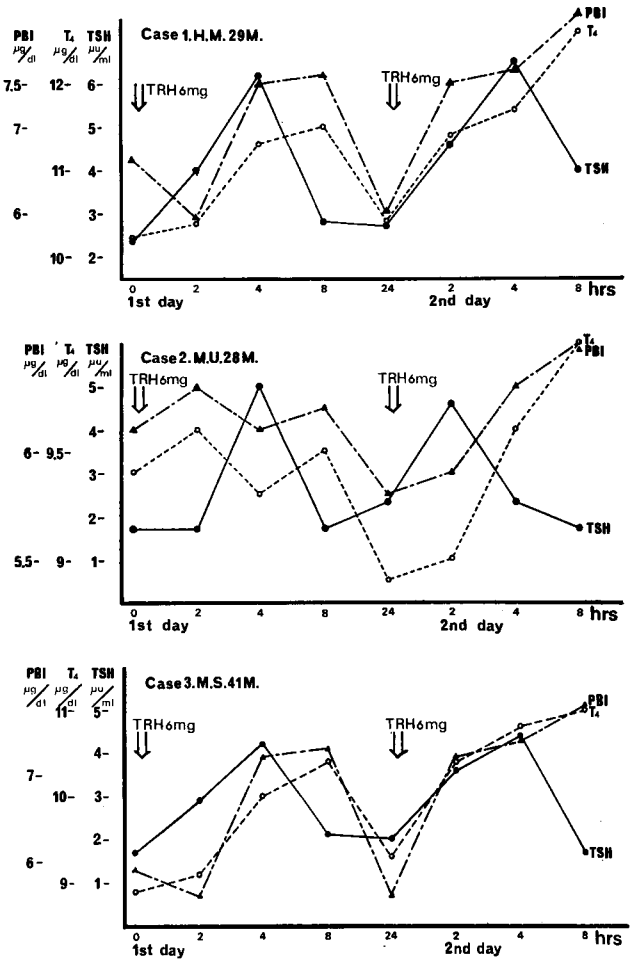

Fig. 1 Change in plasma TSH and blood thyroid hormones after repeated oral administration of TRH (6 mg, once a day). Arrows indicate the time of TRH administration.

administration. A gradual rise of blood thyroid hormone concentration was observed in case 1 who showed prolonged high level of blood thyroid hormone. Case 3 didn't show any consistent changes of plasma TSH and blood thyroid hormone levels to TRH (Fig. 2).

Thus, there were individual variations of onset, duration and magnitude of pituitary thyroid response in repeated oral administration of TRH. Two mg of TRH was administered twice a day (at 9.00, A.M. 5.00 P.M.) to 3 normal subjects for 3 days. Changes in plasma TSH and blood thyroid hormone were estimated in the same fashion mentioned above. Frequent but short durating TSH rises, with thyroid

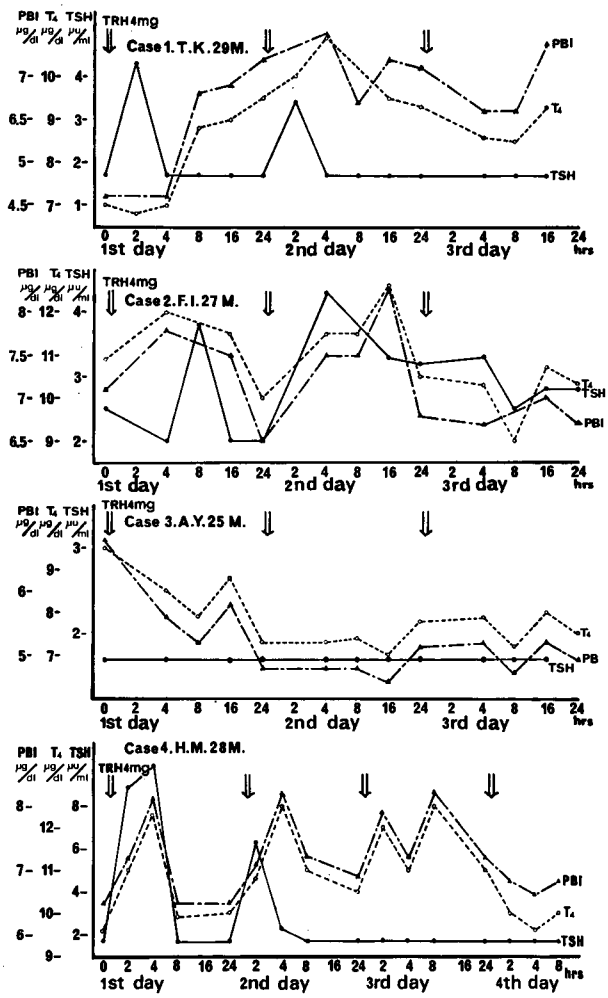

Fig. 2 Change in plasma TSH and blood thyroid hormones after repeated oral administration of TRH (4 mg, once a day). Arrows indicate the time of TRH administration.

hormone increase were obtained in all cases and these hormone increases were almost corresponding for each TRH administration (Fig. 3).

Magnitudes of serum PBI response, represented maximum ⊿PBI (difference between maximum PBI increase and basal PBI), were in 0.4-2.5 μg/dl in 10 cases treated with repeated TRH administration (4 mg or 6 mg, once a day). Singnificant difference ($P<0.05$) was observed between maximum PBI and basal PBI values suggesting that repeated TRH treatment might induce significant PBI increase (Table 2).

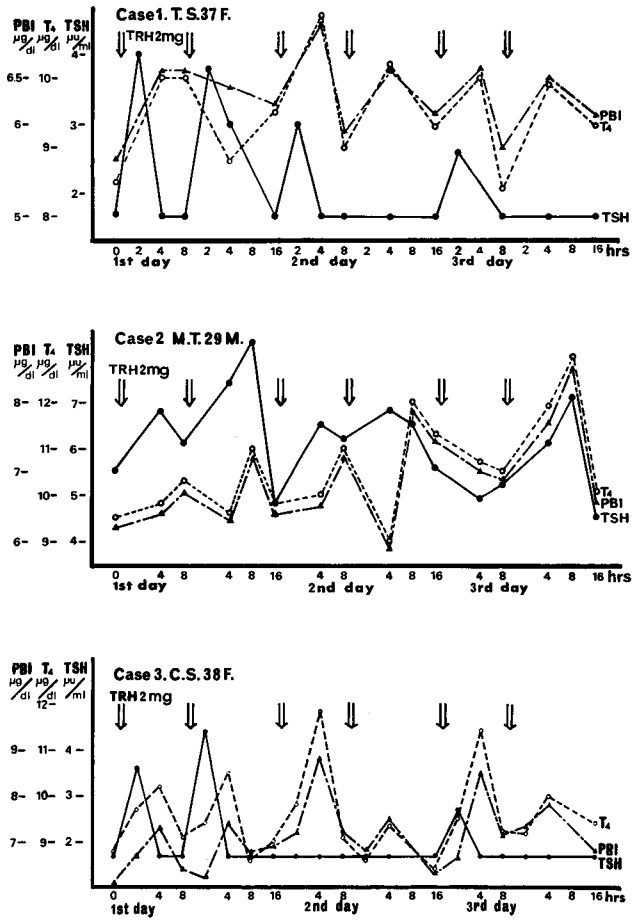

Fig. 3 Change in plasma TSH and blood thyroid hormones after repeated oral administration of TRH (2 mg, twice a day). Arrows indicate the time of TRH administration.

Table 2 Change in serum PBI after repeated oral administration of TRH.

Basal PBI	Max. PBI increment	Max. ⊿PBI
6.5*	8.3*	1.8
4.6	6.5	1.9
4.8	5.2	0.4
6.2	8.5	2.3
5.6	7.1	1.5
5.8	6.5	0.7
5.8	8.3	2.3
Mean 5.6±0.7 (SE)	7.2±0.5 (SE)	*μg/dl
Basal PBI vs Max. PBI	$0.01 < P < 0.05$	

3. Effect of repeated oral administration of TRH in patients with hypothyrotropic hypothyroidism

The effect of repeated oral TRH administration in hypothyrotropic hypothyroidism is illustrated by the case histories which follow.

Case 1. M.K., ectopic pinealoma

A 26-year-old male complained of thirst sensation and polyuria of 16 years duration with a 10 years history of sexual immaturity which is complained as infantile appearance of male gonades. 14 years previously, at the age of 12, the patient noted disturbance of visual acuity and anoymous hemianopsia. Craniotomy was performed because of his progressive visual disturbance at the age of 16 and revealed a ectopic pinealoma (pinealoblastoma) occupying chiasmatic region and floor of 3rd ventricle. Since he received radiation therapy of 2750 γ after surgery, his visual acuity had improved, however, no remarkable improvement of polyuria and hypogonadism was observed. Laboratorical studies showed that patient's hypotonic polyuria (4,000-5,000 ml/day) could not be modified either with water deprivation or intravenous infusion of hypertonic saline, but was easily terminated by the subcutaneous administration of 20 units of aqueous vasopressin. His serum total cholesterol and triglyceride had risen to 315 and 219 mg/dl respectively. Both of urinary 170HCS and 170S excretion rates as well as plasma cortisol level were noted to be low. Almost blunted LH and GH responses were obtained in LH-RH test and in insulin induced hypoglycemia test. Thyroid function test showed low PBI, T_4, T_3, BMR and TSH levels as indicated in Table 3 with normal PBI response to TSH and normal TSH response to TRH indicating that patient's hypothyroidism might be postulated as hypothalamic hypothyroidism which was

Table 3 Endocrine findings of cases with suspected hypothalamic hypothyroidism who were treated with oral administration of TRH.

Subject / Diagnosis	M.K. 25 M Ectopic pinealoma						I.N. 38 M Craniopharyngioma						Y.Y. 16 M Dwarfism, Diabetes insipidus						
Urinary 170HCS (mg/day)	0.5	0.2	0.1	0.9	0.8		4.4		5.8		7.1		2.1						
170S (〃)	0.1	0.1	0.1	3.2	2.5		0.2		0.6		0.6		1.4						
Metyrapon test (Metyrapon 3.0 g p.o.)								0			24°				0	24°		48°	
							plasma ACTH(pg/ml)	Metyrapon 0		1.5 g		10.0	170HCS	0.6		8.6		6.1	
Plasma 110HCS (μg/dl) (ITT)	0′	30′	45′	60′	90′	120′													
	2.2	5.6	7.6	5.6	1.0	3.0	0′	30′	45′	60′	90′	120′	0	15′	30′	45′	60′	90′	120′
HGH (mμg/ml) (ITT)	0.6	0.5	1.3	0	0	0.7	2.7	1.2	1.4	1.1	1.5	1.7	0.3	0.3	0.3		0.2	0.3	0.3
Blood sugar (mg/dl) (ITT)	84	32	70	75	77	71	57	10	12	16	32	40	88	63	55		78	73	68
LH-RH test (mIU/ml) LH	17	17	22	16	24	17	2.5	5.0	4.0	2.0	3.0	1.5	25.0		32.0	29.0	29.0	21.0	19.5
FSH	<5	11	13	13	11	10													
BMR (%)	−25		−19		−25		−40		−36				−5						
PBI (μg/dl)	4.8		1.8		1.4		3.4		2.6				4.19		4.0				
Total T_4 (μg/dl)	1.4		2.4		^{131}I upatke 17.7%		3.4		T_3 0.6ng/ml				7.75 (T_4-I 5.06)						
T_3 RSU (%)	21.9		22.6				25.1						22.9						
TSH test (Thytropar 10USP)		0	24°	48°				0	24°	48°									
	PBI	1.8	2.0	2.0 (μg/dl)															
	T_4	1.4	1.7	2.8 (〃)				3.4	6.4	5.5									
TRH test	0	15′	30′	60′			0	10′	15′	20′	30′	60′		0	15′	30′	60′		
(TRH 50μg)	1.7	18.5	18.5	12.5 (μU/ml)									50μg	2.8	3.2	3.0	1.7		
(TRH 100μg)	1.7	5.6	9.6	6.3*(〃)*			1.7	22.8		20.1	25.1	28.1	100μg	3.5	6.1	6.3	4.0		
Serum total cholesterol (mg/dl)	315						239						236						
Others	Diabetes insipidus Plasma cortisol 0.9 μg/dl (9.00 A.M.)						Plasma testosterone 15 ng/dl						Diabetes insipidus Urinary total gonadotropin 12 μ/day						

*Under treatment with dessicated thyroid powder.

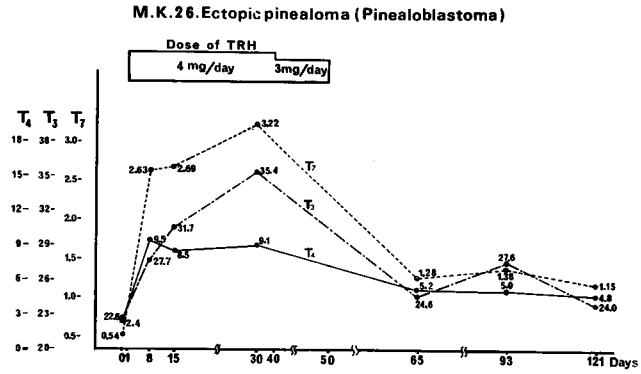

Fig. 4 Effect of repeated oral administration of TRH on pituitary-thyroid function in a patient of ectopic pinealoma (M. K. 26 years, male).

caused from endogenous TRH deficiency.

TRH treatment (Fig. 4). Two mg of TRH was administered twice a day (9.00 P.M. and 5.00 P.M.) for 40 days to this patient, after that 3 mg of TRH was given for 10 days (2 mg was given at 9.00 A.M., 1 mg at 5.00 P.M.). A significant rise of serum T_4, T_3 and T_7 was obtained 1 week after TRH administration from the extremely low level of thyroid function to reaching normal range and this normal level was maintained over next 4 weeks. Though TRH administration was discontinued at the 50th day, T_4, T_3 and T_7 values, remained in about 2 fold to that of before TRH treatment for 70 days after TRH withdrawal. No differences were observed in body temperature, pulse rate, urine volume, liver function, renal function, peripheral blood-cyte counts and serum electrolyte of before and after TRH treatment. A itching erythema of fore and upper arm was noted at 33 days of TRH treatment, but this skin rash vanished after 3 weeks.

Gase 2. I. N., craniopharyngioma

A 38-year-old-male first admitted because of his visual difficulty, impotence and cold intolerance which are appeared at his age of 35 following initial complaint of headache and easy fatiguability. Vertigo and nausea were observed for these 2 years and marked constipation for 1 year. Physical examination revealed hypochromic anemia, edematous appearance of face, moderate dry skin, sinus brady cardia, low voltage in ECG and low body temperature. The elevation of serum β-lipoprotein, triglyceride, total cholesterol and free fatty acid was detected.

By cerebral angiography, mass lesion was suspected on the suprasellar area and through ophthalmologic examination left temporal hemianopsia was proved. The result of endocrinologic examinations is shown in Table 3. The urinary corticoid excretion rate was within normal limilt in several measurements and the level of plasma cortisol changed from the undetectable value to 2.0 μg/dl after i.v. injection of 0.25 mg synthetic ACTH. The level of plasma ACTH did not increase significantly by the single metyrapon test. The response of GH to insulin-induced hypo-

glycemia was poor and the plasma LH level was not increased by synthetic LH-RH. The level of plasma testosterone was noted to be low. As to thyroid functions BMR, PBI, T-$_3$RSU, serum total T_4 and total T_3 were all of low level. The response of plasma TSH to synthtic TRH administration started from the low resting level and increased to normal range, which peaked at 60 minutes. According to the result of TRH test, the hypothalamic hypothyroidism was similarly suspected in this case. He was diagnosed and operated as suprasellar tumor from the results of the above exminations. The tumor occupied upper portion of sella turtica and compressed optic chiasma and hypothalamus. The left optic nerve was thinned by the compression of the tumor. The tumor was walnut size and cystic. Hypothalamus was oppressed remarkably by the tumor, which developed over the turcica. The hard tumor was removed together with the surrounding capsule, and radiation therapy was not performed.

TRH treatment (Fig. 5)

Two mg of TRH was administered orally twice a day for 21 days. The levels of plasma T_4 and PBI, which were low before the therapy, was elevated obviously after the 7th day of TRH administration, and reached into peak at the 14th day.

The level of the plasma T_4 and PBI tends to decrease from the 6th day after the TRH withdrawal but this level was still higher than that before the TRH therapy. On the other hand, the resting level of plasma TSH, which was undetectable before the therapy elevated to 6.9 μU/ml 7 days later. After 14 and 26 days, the plasma TSH level again became to be undetectable. The characteristics of this case were the improvement of the above endocrinologic findings and of the

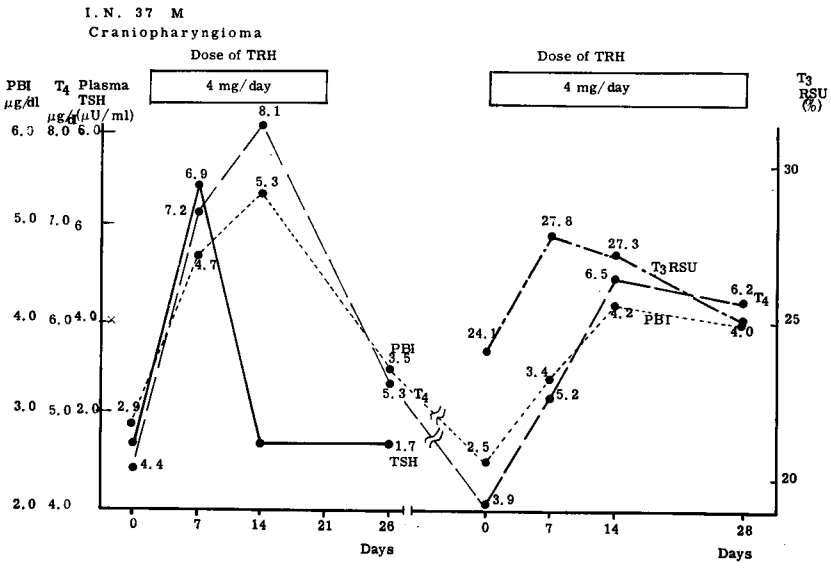

Fig. 5 Effect of repeated oral administration of TRH on pituitary-thyroid function in a patient of craniopharyngioma (I. N. 37 years male).

subjective and objective symptoms, i.e. the appetite improved remarkedly from the 3 to 4th week, dry skin improved, and became talkative. After 3 months' interval, the second administration of TRH was performed for 4 weeks. Reproducible increase of plasma TSH, T_4 and PBI was observed with neuroendocrine improvement described before. This case is under the observation at present.

Case 3. Y.Y., dwarfism and diabetes insipidus

A 16 year-old-male-student first complained of disturbance of height development and polyuria. His birth was normal and his body weight at newborn was 3030 g. He developed after the birth without any abnormalities and began to walk at one year. At 20 months old he had symptoms of fever, vomiting and nucheal rigidity and was diagnosed tuberculous meningitis, and he was treated by the antituberculous agents. After he experienced the tuberculous meningitis he had been developing poorly. His body height developed poorly and was under the standard of the same age. In contrast, his body weight was over the standard. After 14 years of age, polyphagia and polydispia had begun to occur. The body height was 139 cm and body weight was 49 kg.

Abdominal subcutaneous fat was developed remarkably. No axillar and pubic hair were found. On external sexual organs, the penis was the length of 2.5 cm and was phimotic, both testicles were palpable. The amount of urine was about 3,000 ml per day and the specific gravity of urine was 1.002-1.008.

The value of total serum cholesterol was 236 mg/dl. On visual field and opthalmoscopic examination were no abnormalities.

Examination of cerebrospinal fluid was normal. The results of endocrinologic examination were showed in Table 3. The abililty of water concentration was disturbed. Urinary excretion of corticoid was in low level, but increased by the administration of metyrapon. Urinary excretion of corticoid by injection of synthetic ACTH was increased apparently. The level of serum GH to insulin-induced hypoglycemia did not augment entirely. The level of plasma LH after intraveous injection of synthetic LH-RH hardly changed. The low gonadotrophin levels in urine were found. On thyroid function, the values of BMR, PBI and serum T_4 were between subnormal level and low level.

T_3-RSU was low apparently and ^{131}I-uptake was low (13.6%) at 3 hours. The response of plasma TSH after injection of 50 μg synthetic TRH was poor in which the peak level did not elevate to normal response range. But after injection of 100 μg synthetic TRH the levels of plasma TSH was elevated to normal range. This patient, similarly to the case I.N., was administered 2 mg of synthetic TRH orally twice a day for 21 days. The level of serum T_4 and PBI was increased gradually in 7 days to 14 days after the administration, and reached into the peak at the 14th day. T_3-RSU was increased apparently from 22.9% before the administration to 31.8% after the 21st day. ^{131}I-uptake was increased from 13.6% to 19.4% at 3 hours. Resting level of plasma TSH was gradually increased from undetectable level to 2.8 μU/ml at the 7th day and to 3.2 μU/ml at the 14th day (Fig. 6).

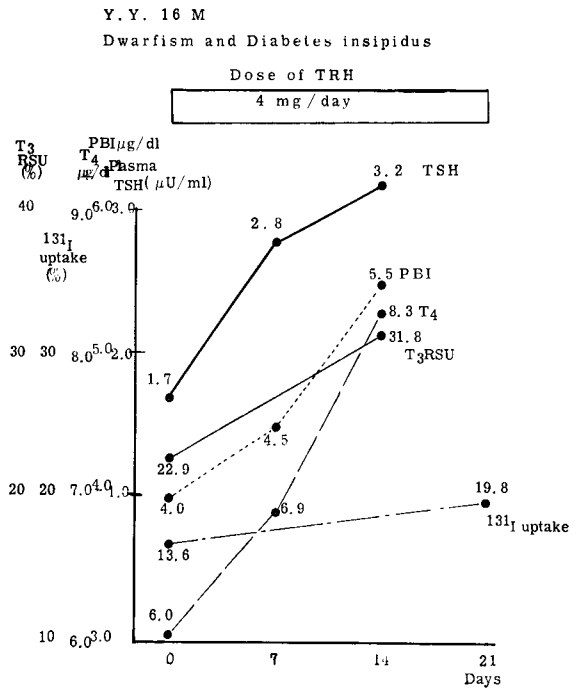

Fig. 6 Effect of repeated oral administration of TRH on pituitary thyroid function in a patient of dwarfism and diabetes insipidus (Y. Y. 16 years, male).

DISCUSSION

Thyrotropic effect (accerelation of thyroid hormone secretion) of TRH would be required firstly in the studies of therapeutic application of TRH. Thyrotropic effect of TRH, however, had not been completely determined throughout enteral or parenteral TRH administration. A short durating rise of serum T_4,[1, 9] T_3 [9] and PBI[7, 13] was observed by intravenous single push of TRH in doses of 50-800 μg. On the contrary, other observatiotions revealed that the thyrotropic effects of TRH were not consistently observed by parenteral administration. Oral TRH administration is thought to be suitable for the purpose of therapeutic application of TRH, because long durating thyroid hormone increase might be expected. Faglia[1] had reported the thyrotropic effect of single oral administration of TRH in which 20 mg of TRH induced plasma TSH rise in level of 22-42 μU/ml at 120-140 minutes after administration and also evoked serum T_4-I net increase in level of 3.5-17.5 μg/dl. The peaks of T_4-I increase were obtained at 180-240 minutes after oral TRH administration. Ormston [11] also reported that oral minimum effective dose was 1 mg, and 40 mg of TRH was required for consistent rise of serum PBI level. Effective dosages of TRH in therapeutic application were determined from our previous observation of single oral administration in which plasma TSH increase

was obtained at 2-4 hours after single administration of 3, 4, 5 and 10 mg of TRH and serum T_4 level also rose at 6-8 hours after single administration of 3 mg and more. As to repeated administration, 4 mg or more of TRH is thought to be necessary for significant rise of plasma TSH and blood thyroid hormone concentration. Also no differences in magnitude of TSH and thyroid hormone increase were observed between the effect of TRH administration of 4 mg once a day and that of 2 mg twice a day.

However, frequent thyroid hormone increase was available by the administration of 2 mg twice a day, while administration of 4 mg once a day induced only an infrequent thyroid hormone response. From these results, mode, dosage and duration of TRH treatment were tentatively determined and performed to hypothyrotropic hypothyroidism, though further observation seems to be necessary on mode and dosage of TRH administration. Haigler[4] has shown that repeated oral administration of small dose of TRH induced small but progressive increment of serum T_4. This finding was in good agreement with that of our observation in which repeated administration of 3 or 4 mg of TRH induced accumulative increase of blood thyroid hormones in patients with hypothyrotropic hypothyroidism. However, there were individual variations of blood thyroid hormone increase and its duration after each administration of TRH which might depend on individual thyroid and pituitary responsibility to TRH. Although smaller increase of plasma TSH or blood thyroid hormone was obtained in certain healthy subject, there was individual variation of response, i.e. certain cases showed smaller increase of TSH and thyroid hormone to later TRH administration, while the other cases responded with almost equal hormone increase to repeated TRH administration. Similar findings were found by Haigler[5] and further observation on this phenomenon seems to be necessary in future. These difference of pituitary thyroid responses might be caused from both individual contents of intrapituitaric TSH and individual magnitude of blood thyroid hormone increase which acts on pituitary thyrotroph to inhibit the TSH release by TRH. This interpretation indicates that rather small dose of TRH might be suitable for therapeutic application of TRH.

From the findings of our observation, repeated administration of TRH was thought to be effective sepecially for hypothyrotropic hypothyroidism which was noted to be both form of hypothalamic and pituitary origin. Patients of hypothalamic hypothyroidism might be postulated as first or absolute indication of TRH treatment, because they have a sufficient pituitary TSH reserve to TRH. Pituitarigenic hypothyroidism includes both type of complete TSH deficiency and partial TSH deficiency; the latter has a limited pituitary TSH reserve which is checked by TRH test. Partial pituitary TSH deficiency might be postulated as second or relative indication of TRH treatment.

M. K. case of ectopic pinealoma and I. N. case of craniopharyngioma were diagnosed as hypothalamic hypothyroidism from their hypothyroid functions, low levels of resting TSH and normal TSH responses to TRH which showed sufficient pituitary TSH reserve. Y. Y. case was suspected as partial pituitary TSH deficiency, because both thyroid function and resting TSH level were noted to be low, and TRH induced TSH response was in subnormal range. TRH treatment was quite effetive, as

described before, in these 3 patients of hypothyrotropic hypothyroidism including both type of hypothalamic and pituitary origin. It has been also well documented that advanced stage of pituitary adenoma often belongs to hypothyrotropic hypothyroidim, [2, 8] and low dose of TRH (100 μg) could not induce pituitary TSH release, whereas 400 μg of TRH was effective in releasing TSH in certain patients of pituitary chromophobe adenoma.[17] These findings might indicate that optimal dose of TRH or repeated TRH administration would be effective in releasing TSH even in patients of pituitarigenic hypothyrotropic hypothyroidism with partial TSH deficiency.

TRH treatment might have following advantages comparable to thyroid hormone treatment;

1. Physiological thyrotropic effect (via endogenous TSH) would be expected without pituitary TSH inhibition.

2. Optimal concentration of blood thyroid hormone would be obtained. Extremely high level of blood thyroid hormone might inhibit TRH induced TSH response and this inhibiting mechanism might prevent excessive increase of blood thyroid hormone concentration which has miscellaneous catabolic disadvantages such as coronary accident, hepatic or myocardial damage caused by thyroid hormone treatment.

3. Direct action of endogenous TSH, for example lypolytic action, would be maintained by TRH treatment while thyroid hormone treatment would inhibit the endogenous TSH secretion from the anterior pituitary gland.

There were no remarkable side action of TRH treatment except transient nausea which was observed in 2 cases 30–60 minutes after oral TRH administration. Only one case of ectopic pinealoma showed erythema like skin rash of upper extremities which was vanished 3 weeks after onset, although this skin rash could not be recognized as a side action of TRH, because erythema like skin rash was observed far from 33 days after onset of TRH administration. Jacobs[10] had reported that TRH simultaneously stimulates prolactin release from pituitary gland in man. Estimation of blood prolactin changes would be required in repeated TRH administration for further studies of side action of TRH treatment.

SUMMARY

Clinical observations were performed on the therapeutic applications of TRH.

1. In healthy subjects plasma TSH increase was obtained from 2 to 4 hours after the single oral administration of 4, 5 and 10 mg of TRH. Serum T_4 and PBI levels also rose 6–8 hours after single oral administration in doses of 3 mg and more.

2. Almost all cases showed plasma TSH increase at 2 to 4 hours after each oral administration of TRH which was given orally by 2 to 8 times in doses of 2, 4 and 6 mg.

3. Four mg of TRH was administered daily to 3 patients with hypothyroidism due to craniopharyngioma, ectopic pinealoma and suspected hypopituitarism who showed sufficient pituitary TSH reserve to TRH test. Gradual increases of serum T_4, T_3 and PBI were obtained and these increases reached their peaks 2 weeks after the onset of oral administration.

4. There were no remarkable side action of TRH except transient nausea which was observed in 2 cases 30-60 minutes after oral TRH administration.

5. Further studies on therapeutic application of TRH would be significant for the development of replacement therapy on hypothyrotropic hypothyroidism.

ACKNOWLEDGEMENTS

Grateful acknowledgement is made to prof Dr. H. Ibayashi (Department of Internal Medicine Kyushyu University School of Medicine) and his collaborators for their kind advice and guidance. The authors wish to thank the members of the 2nd the department of internal medicine, Osaka medical college for making the chance to observe the patient of hypothyrotropic hypothyroidism.

REFERENCES

1. Faglia, G., Beck-Pecoz, P. Ambrosi, B. Ferrari, C. and Travaglini, P. Acta Endocr. 1972. 71. 209/225. The effects of a synthetic thyrotropin releasing hormone (TRH) in normal and endocrinopathic subjects.
2. Fleisher, N., Lorente, M. Kirkland, J. Kirkland, R. Clayton, G. and Calderon, M. Endocrinol Metab. 1971. 34. 617.
Synthetic thyrotropin releasing factor as a test of pituitary thyrotropin reserve. J. Clin.
3. Gillessen, D., Felix, A. M. Largier, W. and Studer. R. O. Helv. Chim. Acta. 1970. 53. 63/72. Synthese de des "thyrotropinreleasing" hormone (TRH) and Verwandter peptide.
4. Greenwood, F. C., Hunter, W. M. and Glover, J. S. Biochem. J. 1963. 89. 114/123. The preparation of ^{131}I-labelled human growth hormone of high specific radioactivity.
5. Haigler, Jr. E. D., Pittman, J. A. Jr, Hershman, J. M. and Baugh, C. M. 1971. 33. 573/581. Direct evaluation of pituitary thyrotropin reserve utilizing synthetic thyrotropin releasing hormone. J. Clin. Endocrinol Metab.
6. Haigler, Jr. E. D., Pittman, Jr, J. A. and Hershman, J. M. J. Clin. Endocrinol Metab. 1971. 35. 631/635. Response to orally administered thyrotropin-releasing hormone in man.
7. Hall, R., Amos, J. Garry, R. and Buxton, R. Brit. Med. J. 1970. 2. 274/277. Thyroid-stimulating hormone response to synthetic thyrotropin releasing hormone in man.
8. Hall, R., Ormston, B. J. Besser, G. M. Cryer, R. J. and Mekendrick, M.Lancet, April 1972. 8, 759/763. The thyrotropin-releasing hormone in diseases of the pituitary and hypothalamus.
9. Hollander, C. S., Mitsuma, T. Shenkman, L. Woolf, P. and Gershengorn, M. C. Science 1972. 175. 209/210. Thyrotropin-releasing hormone: Evidence for thyroid response to intravenous injection in man.
10. Jacobs, L. S., Snyder, P. J. Wilber, J. F. Rtiger, R. D. and Dghdday, W. H. J. Clin. Endocrinol Metab. 1971. 33. 996/998. Increased serum prolaction after administration of synthetic thyrotropin releasing hormone (TRH) in man.
11. Ormston, B. J., Kilborn, J. R. Garry, R. Amos, J. and Hall. R. Brit. Med. J. 1971. 2. 199/202. Further observation on the effect of synthetic thyrotropin-releasing hormone in man.
12. Pittman, J. A., Haigler, E. D. Hershman J. M. and Pittman. C. S. Nes. Engl. J. 1971, 285, 844/845. Hypothalamic hypothyroidism.

13. Sakoda, M., Otsuki, M. Hiroshige, N. Kanao, K. Yagi, A. and Honda, M. Endocr. Japon. 1970. 17. 541. Effect of synthetic thyrotropin-releasing factor (TRF) on pituitary TSH secretion in man.
14. Sakoda, M., Otsuki, M. Fukatsu, H. and Baba, S. Folia Endocr. Japon. 1972. 47. 1046/1060. (in Japanese) Effect of thyrotropin-releasing factor (TRF) on pituitary TSH secretion in man.
15. Sakoda, M., Mori, H. Otsuki, M. Fukuda, T. and Baba, S. Kobe J. Med. Sci 1972. 18. 15/19. Neuroendocrine control of the pituitary TSH secretion.
16. Sakoda, M., Mori, H. Otsuki, M. Tateiwa, M. Baba, S. and Fujita, S. Folia Endcor. Japon. 1973. 49. 750/760. (in Japanese) On the clinical picture of hypothalamic hypothyroidism.
17. Sakoda, M., Mori, H. Tateiwa, M. Kusaka, T. Otsuki, M. Fukuda, T. and Baba, S. J. Japan. Soc. Intern. Med. 1973. 62. 1520. On the pituitary TSH response to different dosage of thyrotropin releasing factor (TRF). (in Japanese)
18. Shenkman, L., Mitsuma, T. Suphavai, A. and Hollander, C. S. Lancet,January. 1972. 15. 111/113. Triiodothyronine and thyroid-stimulating hormone response to thyrotropin-releasing hormone.