Serum Thyrotropin Response to Thyrotropin Releasing Hormone and the Concentration of Thyroid Hormone in Patients with Hyperfunctioning Thyroid Nodule

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Synopsis

Relationship between serum TSH response to TRH and serum thyroid hormone levels was studied in 8 patients with single hyperfunctioning nodule of thyroid. The results were variable. No or low response to 500 μ g TRH was observed in 6 subjects, 3 of whom were associated with elevated T_4 and T_3 , one with normal T_4 and elevated T_3 and two with normal T_4 and T_3 . Normal response was shown in other 2 subjects with normal T_4 and T_3 . Following administration of 2,000 μ g TRH to 3 subjects with absence of response to 500 μ g TRH, 2 subjects with elevated T_4 and T_3 showed no response, but one with normal T_4 and T_3 showed low but definite response. After removal of the nodule, TSH response to TRH was increased in 3 subjects. Two of them was associated with decreased T_4 and T_3 but another one showed negligible changes in T_4 and T_3 . These findings may indicate that responsiveness of TSH to TRH in these patients is not solely dependent on circulating thyroid hormone levels.

A hyperfunctioning nodular goiter is characterized by hyperfunction of the nodular tissue associated with hypofunction of the remainder of the normal tissue. Such a state is demonstrable by thyroid scanning. Radioiodine accumulation of the normal area when it remains, is suppressed, by thyroid hormone or when it is suppressed, it is restored by TSH, while that of the nodular area is unchanged (Sheline and McCormack, 1960). These findings suggest that the autonomous nodular tissue produces excess thyroid hormone which in turn suppresses the function of the remaining normal thyroid tissue by negative feedback mechanism. Recently, synthetic thyrotropin-releasing hormone (TRH) has been used for the evaluation of TSH secretion in man. Lack of response of serum TSH to TRH administration has been shown in some thyroid disorders,

such as diffuse toxic goiter (Kumahara *et al.*, 1971; Lawton *et al.*, 1971; Ormston *et al.*, 1971; Shenkman *et al.*, 1973) or subacute thyroiditis during acute phase (Ogihara *et al.*, 1973). As an analogy of these thyroid disorders, Karlberg (1973) and Ridgway *et al.* (1973) has demonstrated an absent TSH response to TRH in patients with single thyroid nodule, either in hyperthyroid or even in euthyroid state. Although triiodothyronine (T_3) has been known to be an important modulator of responsiveness to TRH (Snyder and Utiger 1972a; Shenkman *et al.*, 1973), serum T_3 concentration has been found to be normal (Ridgway *et al.*, 1973).

In the present study, pituitary responsiveness to TRH was examined in patients with solitary hyperfunctioning thyroid nodule in various thyroid conditions including that before and after removal of the nodule, and the relationship between their responsiveness to TRH

and thyroid states judged by serum thyroxine (T_4) and T_3 were discussed.

Materials and Methods

Eight patients with solitary hyperfunctioning nodule of the thyroid were studied. Their thyroid states are summarized in Tables 1 and 2.

TSH response to TRH was determined as previously described (Kumahara *et al.*, 1971). TRH used in this study was synthesized by Dr. Shinpei Sakaki-

bara, Peptide Institute, Protein Research Foundation, Osaka, and the preparation for injection was prepared by Tanabe Seiyaku Co., Ltd. Blood was withdrawn before, 30, 60 and 120 min after intravenous injection of 500 μ g of TRH. In 3 cases, 2000 μ g of TRH was given separately. Radioimmunoassay of TSH was performed by the double antibody method as described by Patel *et al.* (1971) using a commercial kit of Daiichi Radioisotope Laboratories (reagents were provided from Calbiochem.). Serum T_3 was measured by radioimmunoassay according to Lieblich and Utiger (1972) using anti- T_3 rabbit serum which was made in our laboratory. The thyroid function tests

Table 1. Scintiscanning and histological findings of patients with hyperfunctioning thyroid nodule.

Subjects	Age, Sex	Extirpation of nodule	Goiter Size (cm)	Scintigram	Histological findings of nodule
1. T.K.	39, F	before	4.0 $\times$ 2.5	left hot nodule diffuse uptake after TSH	
2. S.Y.	50, F	before	5.0 $\times$ 3.5	left hot nodule diffuse uptake after TSH	
3. S.G.	64, M	before	5.4 $\times$ 4.0	left hot nodule diffuse uptake after TSH	tubular adenoma with adenomatous cystic goiter
4. K.S.	21, F	after (1 mo.) before	3.5 $\times$ 3.5	diffuse uptake by right side middle-hot nodule diffuse uptake after TSH	tubular adenoma
5. Y.S.	62, F	after (1 mo.) before	3.0 $\times$ 3.0	diffuse uptake left hot nodule diffuse uptake after TSH	
6. M.K.	23, F	before	4.0 $\times$ 2.0	right warm nodule hot nodule after T_3	follicular adenoma
7. S.S.	40, F	after (4 mo.) before	2.8 $\times$ 1.8	diffuse uptake by left side right warm nodule diffuse uptake after TSH	adenomatous goiter
8. S.O.	49, F	after (8 mo.) before	4.2 $\times$ 3.0	diffuse uptake by left side left warm nodule left hot nodule after T_3 diffuse uptake after TSH	

mo: month.

Table 3. TSH response to 500 μ g and 2,000 μ g TRH administration

Subjects	Dose of TRH (μ g)	TSH (μ U/ml) after TRH			
		0	30	60	120 min
1. T.K.	500	<1.0	<1.0	<1.0	<1.0
	2,000	<1.0	<1.0	<1.0	<1.0
2. S.Y.	500	<1.0	<1.0	<1.0	<1.0
	2,000	<1.0	<1.0	<1.0	<1.0
5. Y.S.	500	<1.0	<1.0	<1.0	<1.0
	2,000	<1.0	4.3	3.2	3.5

were performed using the standard procedures as follows: basal metabolic rate (BMR) by Sanborn's metabulator, T_4 by competitive protein binding analysis using Tetralute kit (Ames Co.), ^{131}I - T_3 resin sponge uptake (RT_3U) by Triosorb test kit (Dainabot Radioisotope Laboratories). The normal values of these tests in our laboratory are listed in Table 2.

Results

As shown in Table 2, results of serum TSH response to TRH and the thyroid function tests were variable. The basal levels of serum TSH were negligible and did not rise to normal limits after 500 μg TRH administration in 6 subjects; cases 1–3 with elevation in both serum T_4 and T_3 , case 4 with normal T_4 and elevated T_3 , and cases 5 and 6 with normal T_4 and T_3 . In the other 2 subjects (cases 7 and 8) with normal T_4 and T_3 , basal TSH was detectable, and normal responses to TRH were observed. Thyroid scintiscans disclosed hot nodule in cases 1–5 without response to TRH and warm nodule in cases 6–8 with response to TRH (Table 1). As shown in Table 3, administration of 2000 μg TRH did not cause response of TSH in cases 1 and 2 with elevated T_4 and T_3 but caused definite response in case 5 with normal T_4 and T_3 .

After surgical extirpation of the nodule, TSH response to TRH was significantly increased in 3 out of 4 subjects. (Table 2) In case 3, low but definite response to TRH with decreased T_4 and T_3 1 month after operation became supernormal response to TRH with normalized T_4 and T_3 after 6 months. In case 4, response to TRH and serum levels of T_4 and T_3 were normalized after 6 months. In case 6, response to TRH was increased with slight or negligible changes in T_4 and T_3 .

Discussion

Lack of TSH response to TRH was observed in patients with hyperfunctioning thyroid nodule, with elevated T_4 and even with normal

T_4 . Karlberg (1973) has also demonstrated no response to TRH in clinically euthyroid patients with normal T_4 , and he suggested T_3 -hypersecretion in such patients. It is also considered that thyroid adenomas may secrete more T_3 than T_4 (Hollander *et al.*, 1972) although T_3 content in the adenomas tissue was not found to be increased (Larsen *et al.*, 1973). Present work has demonstrated a patient with " T_3 toxicosis" without response to TRH. The finding is consistent with a hypothesis that circulating T_3 is an important modulator of pituitary responsiveness to TRH (Shenkman *et al.*, 1973). The reason why cases 1–3 had normal RT_3U remains unclear.

On the other hand, 2 patients (cases 5 and 6) showed no or low response to TRH in spite of the normal concentration of circulating T_4 and T_3 . The free T_4 and T_3 concentrations have been found to be normal in such subjects (Ridgway *et al.*, 1973). There was no dose related response beyond a dose of 400 μg TRH in normal man (Snyder and Utiger 1972b). In case 5, however, there was no response to 500 μg TRH but a definite response to 2000 μg TRH. Bowers *et al.* (1967) demonstrated that increasing the dose of TRH overcome the inhibition caused by T_4 in mice. It is suggested that only minimal increases in thyroid hormone concentration in blood and/or pituitary gland inhibit TSH response to TRH in these subjects. There was no differences in age, sex, duration of illness, size and histological findings of goiter between responders (cases 7 and 8) and non-responders (cases 5 and 6).

After removal of the nodule, T_4 and T_3 levels decreased and response to TRH increased, but the course was variable. In case 6, response to TRH was significantly increased after operation but changes in T_4 and T_3 levels were slight or negligible. One possible explanation for this phenomenon is that, before operation, an excess amount of thyroid hormone which is secreted from the autonomous nodule causes inhibition of TSH secretion and in turn suppresses production of thyroid hormone by the remainder of the

Table 2. TSH response to TRH and thyroid function in patients with hyperfunctioning thyroid nodule.

Subjects	Extirpation of nodule	TSH (μ U/ml) after TRH (500 μ g iv)				Thyroid function tests				
		0 ($<1.0 \sim 8.0$)	30 ($8.0 \sim 30.0$)	60	120 min	T ₄ (μ g/100 ml) (5.0 $\sim$ 10.0)	T ₃ (ng/100 ml) (95 $\sim$ 200)	RT ₃ U (%) (24 $\sim$ 37)	BMR (%) (-10 $\sim$ 15)	¹³¹ I uptake (%) (10 $\sim$ 40)
1. T.K.	before	<1.0	<1.0	<1.0	<1.0	14.4	260	33	+22	—
2. S.Y.	before	<1.0	<1.0	<1.0	<1.0	10.7	270	35	+35	—
3. S.G.	before	<1.0	<1.0	<1.0	<1.0	12.8	255	26	—	18.0
	after (1 mo.) (6 mo.)	3.2 12.8	5.0 46.7	6.0 65.2	5.0 69.3	2.9 5.3	71 145	24 23	— —	11.8 —
4. K.S.	before	<1.0	1.4	1.4	<1.0	9.8	279	30	+19	43.0
	after (1 mo.) (6 mo.)	2.0 <1.0	20.0 12.0	15.5 16.5	7.2 10.3	3.5 5.7	160 165	25 27	— —	36.6 —
5. Y.S.	before	<1.0	<1.0	<1.0	<1.0	8.5	150	27	+4	35.4
6. M.K.	before	1.1	3.6	2.9	1.4	7.9	171	25	-5	—
	after (4 mo.)	<1.0	18.0	11.0	5.2	8.2	160	28	—	—
7. S.S.	before	1.8	9.4	6.4	3.3	9.4	175	27	+2	27.4
	after (8 mo.)	<1.0	12.4	11.0	7.4	8.4	176	28	—	8.5
8. S.O.	before	2.1	10.7	7.7	4.9	6.7	175	24	+12	28.0

() normal range, mo.: month, <: undetectable

normal thyroid tissue, thus the total thyroid hormone secretion does not so increase, whereas after operation, thyroid hormone was secreted from the normal thyroid tissue under stimulation of TSH, thus the thyroid hormone level does not so decrease. Changing in pattern of the scintigram before and after operation also indicates such a situation. It is also noticeable that the TRH test is useful to detect an abnormal state in which the thyroid hormone is secreted from abnormal thyroid tissue such as hyperfunctioning nodule or ectopic thyroid, or the normal thyroid is stimulated by an extra-pituitary thyroid stimulator such as human chorionic thyrotropin, ectopic thyrotropin, or by a long acting thyroid stimulator.

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