A kinetic study on secretion and elimination of endogenous thyrotropin in the thyrotropin-releasing hormone test

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Serum thyrotropin (TSH) concentrations in normal young men were measured by a high-sensitivity immunoradiometric assay before and after intravenous administration of 500 μg of TSH-releasing hormone (TRH). A kinetic model was applied to evaluate the secretion rate both before (V_0) and after (V_0+V^* at maximum rate) the administration of TRH, the elimination constant (K), the latent time (L) between TRH administration and start of the stimulated secretion, and the total amount of TSH (T) released in response to TRH. V_0, V^* and T varied widely from individual to individual, but correlated well with TSH before TRH administration (r=0.93, 0.80 and 0.87, respectively). A few minutes (1.89$\pm$1.30 min) after the administration of TRH, the secretion of TSH (0.025$\pm$0.016 μU/min ml) was stimulated, and the total release over about 1 h was 12.5$\pm$5.6 μU/ml. Serum TSH was maximum at 31.5$\pm$5.7 min. The half-time of disappearance of TSH was 42$\pm$9 min. These data confirm that the stimulated secretion continues for more than 30 min, and that the pituitary releases 43.2$\pm$22.9 mU of TSH (assuming the distribution volume of TSH is 5.8% of body weight) in response to TRH, an amount which correlates closely (r=0.91) with TSH before TRH administration.

Key words: Kinetic study, TSH secretion, TRH test, High sensitivity RIA

INTRODUCTION

MANY STUDIES on the TSH release response of the pituitary to intravenous injection of TRH have already been published. TSH, response to TRH is reported to be higher in females than in males[1,2] and in females higher in the preovulatory phase than in the postovulatory phase of the menstrual cycle.[2] Snyder and Utiger[3,4] reported that the maximum increase in serum TSH following TRH administration increased in proportion to the TRH dose within the range 6.25–400 μg, diminished significantly with increasing age in males, and was not age-dependent in females. They also reported that there was no difference in the TSH response between males and females when their height and weight were matched.

Some important parameters of TSH regulation in the TRH test remain unknown, but can be found from kinetic considerations. For example, the real amount of TSH released in response to TRH administration, which should correlate closely with the TSH secretory ability of the pituitary; the secretion and elimination rates of endogenous TSH; the latent time between TRH injection and the start of the stimulated secretion of TSH from the pituitary; the pattern of stimulated secretion of TSH, and so on. However, there are already a few kinetic studies on the TRH test. In 1986, Swartz et al.[5] applied a kinetic model to the TRH test, and evaluated some parameters. They discussed the increase in TSH over the baseline, and reported that the latent time after TRH administration was 9.1$\pm$3.7 minutes. But other reports show an increase in TSH within 5 min after TRH administration.[2,3,6]

In this study, we performed the TRH test on 12 normal young men. To obtain the parameters described above, we derived a theoretical expression

for serum TSH by constructing a kinetic model. This model resembles that of Swartz et al.,[5] but we dealt with serum TSH itself while they dealt only with the increase in TSH level over the baseline. Serum TSH before and after TRH was measured by a recently developed high-sensitivity immunoradiometric assay, and the secretion and elimination rates of endogenous TSH, the total amount of TSH released in response to TRH administration, and the latent time after TRH administration were estimated by least squares fitting.

MATERIALS AND METHODS

Subjects

Twelve normal young men, aged 23–33 yr, volunteered for the study. None of them had a history of thyroid disease, and none had any illness or was taking any medication known or suspected to affect thyroid function. All tests were performed in the morning after an overnight fast. 500 μg of synthetic TRH (Takeda) was injected into the antecubital vein at time 0. Blood was sampled at -10, 0 (before TRH), 3, 6, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, 160, 200 and 240 min for determination of TSH. At -10 min, blood was also taken to determine T_3 and T_4.

Assays

Serum TSH was assayed with a commercially available immunoradiometric assay kit (TSH RIABEADS II; DAINABOT: sensitivity 0.1 μU/ml). All samples from an individual subject were analyzed in duplicate in a single assay. With respect to the kit, the intra-assay variance was less than 3%, and the inter-assay variances for control serums containing 1.7 and 7.5 μU TSH/ml were 5% and 3%, respectively.

T_3, and T_4 were measured with commercially available radioimmunoassay kits, T_3 RIABEAD (DAINABOT; sensitivity 0.5 ng/ml) and SPAC T_4 RIA kit (Daiichi; sensitivity 1.0 μg/dl), respectively. All samples were analyzed in duplicate in a single assay. The intraassay variances for the T_3 and T_4 assays were less than 3%.

Kinetic model

Administered TRH is transported to the pituitary, stimulates the synthesis and secretion of TSH,[7] and is eliminated with a half life of 5.3 ± 0.3 min.[6] To describe the variation in the TSH concentration, we constructed a simple kinetic model. This model is based on some assumptions:

1. TSH is eliminated from the blood at a rate proportional to its concentration, with an elimination constant K (min^{-1}).

2. L minutes after the TRH injection, TSH

release is stimulated from its normal rate v_0 (μU/min) to a maximum rate of v_0+v^* (μU/ml).

3. The stimulated rate of TSH release from the pituitary drops back to v_0 at a rate proportional to its instantaneous value with the decay constant R (min^{-1}).

4. The volume of TSH distribution V (ml) remains constant before and after TRH administration.

Then the variation in the total amount of TSH distributed everywhere but in the pituitary, X (μU), is expressed as

$$\frac{dx}{dt}=v-KX \qquad (1)$$

where v is the secretion rate of TSH from the pituitary, i.e.,

$$v=v_0 \qquad\qquad (t<L) \qquad (2)$$
$$=v^*e^{-R(t-L)}+v_0 \qquad (t\geq L) \qquad (3)$$

From equations (1)—(3), we get the following expressions for X.

$$X=\frac{v_0}{K} \qquad\qquad (t<L) \qquad (4)$$

$$=\frac{v^*}{K\text{-}R}\{e^{-R(t-L)}-e^{-K(t-L)}\}+\frac{v_0}{K}$$
$$\qquad\qquad (t\geq L) \qquad (5)$$

Introducing rates of release per unit volume of distribution V^* ($=v^*/V$) and V_0 ($=v_0/V$) (μU/ml min) the serum TSH concentration C (μU/ml) is given by

$$C=X/V=\frac{V_0}{K} \qquad (t<L) \qquad (6)$$

$$=\frac{v^*}{K\text{-}R}\{e^{-R(t-L)}-e^{-K(t-L)}\}$$
$$+\frac{V_0}{K} \qquad\qquad (t\geq L) \qquad (7)$$

Theoretical serum TSH concentrations were calculated from equations (6) and (7) by least squares fitting taking K, R, V^*, V_0 and L as five adjustable parameters. A Simplex method[8] was used.

The total amount of TSH released in response to TRH injection, T (μU/ml), was calculated from the following equation.

$$T=\int_L^\infty V^*e^{-R(t-L)}\,dt=\frac{V^*}{R} \qquad (8)$$

The time at which C becomes the maximum concentration, $Tmax$, is written as

$$T_{\text{max}}=\frac{ln\ K-ln\ R}{K-R}+L \qquad (9)$$

All calculations were performed with a NEC PC-9801 personal computer.

Table 1 Height, weight, age and measured TSH, T_3 and T_4 concentrations

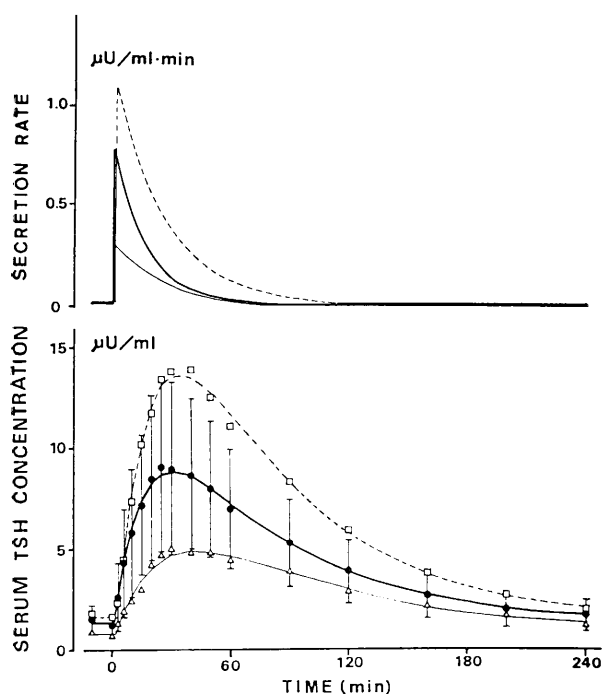| Subject	Age yr	Height cm	Weight kg	TSH[a] $\mu U/ml$	T_3 ng/ml	T_4 $\mu g/dl$
A	31	165	52	0.55	1.1	7.4
B	22	170	58	0.95	1.6	6.9
C	33	164	62	1.9	1.0	5.3
D	27	168	57	1.7	1.2	5.6
E	25	173	62	0.45	1.2	7.4
F	24	164	57	2.25	1.2	5.8
G	24	168	57	0.8	1.3	7.6
H	32	170	52	1.25	1.4	7.5
I	28	174	62	2.1	1.4	7.0
J	25	181	65	0.9	1.4	6.2
K	31	172	64	1.6	1.5	9.8
L	27	168	67	2.7	1.4	8.0
Mean±SD	27.4±3.6	169.8±4.8	59.6±4.9	1.43±0.72	1.3±0.2	7.0±1.2

a: Mean of concentrations at -10 and 0 min.

Fig. 1 Upper panel: secretion rates calculated from the kinetic model. Lower panel: measured and calculated serum concentrations of TSH. Closed circles and vertical lines represent the mean and SD for 12 subjects, respectively. Dark line (————) is the mean for all subjects. Individual data for subjects D (□: ------) and G (△: ———) are also shown.

RESULTS AND DISCUSSION

Height, weight, age and measured TSH, T_3, and T_4 concentrations in the 12 subjects are summarized in Table 1.

The measured TSH concentrations and their SD, the simulated theoretical curve, and the increased releasing rate of TSH are shown in Fig. 1. Simulations were performed with respect to individuals and to the mean values of all subjects.

The values for the determined parameters are summarized in Table 2, together with the calculated maximum TSH concentration C_{max}. With respect to subjects B and K, the values for L were estimated to be less than 0. Therefore, the calculation was performed with a fixed value for L (=0). The values for R and K varied little among subjects, while the values for V_0 and V^* varied widely from individual to individual. The dependence of these parameters on the calculated TSH concentration was demonstrated by the data of subjects D and G in Fig. 1, which were examples of relatively high and low releasing rates, respectively. The measured TSH levels of subjects D and G were plotted together in Fig. 1.

TSH concentrations before TRH injection, TSH_0, correlated with C_{max}, T, V_0 and V^* (r=0.88, 0.87, 0.93 and 0.80, respectively). V_0 correlated with C_{max}, T and K (r=0.76, 0.80 and 0.79, respectively). V^* correlated with T (r=0.88), and C_{max} correlated closely with V^* and T (r=0.96 and 0.97, respectively). Dose (500 μg/weight) dependence was not observed with respect to any parameters.

Considering the time required for TRH to be transported from the antecubital vein to the pituitary, and for TSH to be transported from the pituitary to the antecubital vein, the estimated value for L (1.89±1.30 min) is reasonable, and the stimulated secretion can be considered to begin immediately after the arrival of TRH. This conclusion is different from that of a previous report. Swartz et al.[5] estimated L to be 9.3 min using a kinetic model that resembles ours. They dealt only with the increase in the TSH concentration over baseline, and did not

Table 2 Evaluated values for each subject and all subjects

Subject	V_0 μU/ml min	V^* μU/ml min	K /min	R /min	L min	T μU/ml	T_{max} min	C_{max} μU/ml
All	0.0208	0.75	0.0156	0.0626	1.28	12.0	30.9	8.9
A	0.0083	0.41	0.0149	0.0659	1.65	6.2	30.9	4.6
B	0.0170	0.85	0.0174	0.0865	0[a]	9.8	23.2	7.5
C	0.0508	0.80	0.0259	0.0533	2.23	15.0	28.5	9.5
D	0.0288	1.06	0.0173	0.0509	2.78	20.8	34.9	13.6
E	0.0058	0.25	0.0129	0.0585	2.89	4.3	36.1	3.1
F	0.0364	1.36	0.0163	0.0791	2.27	17.2	27.5	13.6
G	0.0099	0.29	0.0124	0.0426	1.90	6.8	42.8	4.9
H	0.0165	0.97	0.0133	0.0661	2.52	14.7	32.9	11.1
I	0.0389	0.56	0.0209	0.0411	4.20	13.6	37.7	8.7
J	0.0163	0.66	0.0168	0.0683	2.26	9.7	29.5	7.1
K	0.0235	0.74	0.0151	0.0686	0[a]	10.8	28.3	8.7
L	0.0494	1.71	0.0175	0.0795	0.00	21.5	24.4	16.8

Mean±SD 0.0251±0.0156 0.81±0.43 0.0167±0.0037 0.0634±0.0145 1.89±1.30 12.5±5.6 31.4±5.7 9.1±4.1
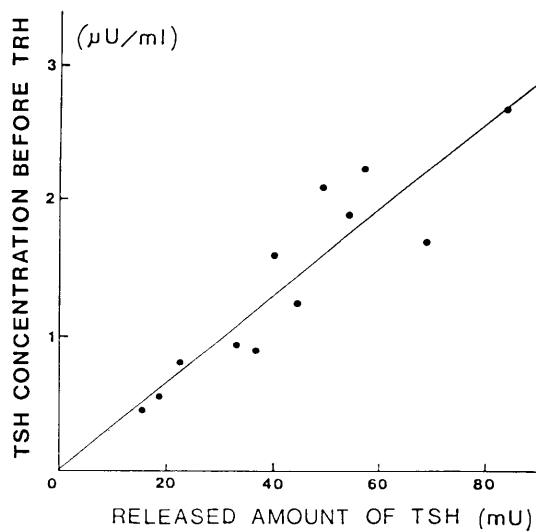a; L was fixed at 0.

Fig. 2 Correlation between TSH concentration before TRH and released amount of TSH. Released amounts were calculated from values of T assuming the distribution volume of TSH is 5.8% of body weight. The correlation coefficient is 0.91.

report the derivation of their expression for the TSH concentration. We consider this discrepancy as probably caused by the large intervals between samples. They collected blood samples only at 0, 15 and 30 min prior to the maximum concentration of TSH.

As shown in Fig. 1, stimulated secretion of TSH started within 3 min after administration of TRH, and seemed to continue for more than 30 min. If the stimulated secretion had terminated within a few min, C_{max} would not have appeared around 30 min. 1.89±1.30 min after the administration of TRH, secretion of TSH was increased from 0.0251±0.0156 to 0.84±0.45 ($=V_0+V^*$) μU/ml min, and a total of 12.5±5.6 μU/ml of TSH was released in response

to TRH administration. This means that the amount of TSH released was equal to the amount normally released in 8.3 hours. TRH is supposed to stimulate both synthesis and secretion of TSH.[7] Though it is not known how much TSH is newly synthesized and how much is stored in the pituitary, it seems that most of the released TSH was stored in a complete or nearly complete form, since it was released in a short time.

The released TSH was eliminated with an elimination constant K ($=0.0167\pm0.0037$ min^{-1}); in other words, the half-time of disappearance of TSH was 42 ± 9 min. This value agrees well with that in another report. Odell et al.[9] evaluated the secretion rate and the half-time of disappearance of TSH by administering exogenous human TSH labelled with 131-I. They reported the secretion rate of TSH (165.2 ± 67.4 mU/ day), the volume of distribution of TSH ($5.8\pm2.3\%$ of the body weight), and the half time of disappearance of TSH (53.9 ± 9.2 min). Though it is known that TSH concentrations show a circadian rhythm[10] and a pulsatile secretion pattern,[11] the variation of the TSH concentration during a day is small. Assuming the secretion rate of TSH to be constant and using the reported value for the TSH distribution volume, the secretion rate measured in our study can be rewritten as 124.9 ± 88.0 mU/day, which is in agreement with the study of Odell et al. and Ridway et al. (104.3 ± 41.4 mU/day).[12] In a similar manner, the total amount of TSH released in reponse to TRH is calculated to be 43.2 ± 22.9 mU, which is considered to represent the secretory ability of the pituitary. As mentioned above, this value varied among subjects and correlated well with TSH_0 (r=0.91) (Fig. 2).

In this study, we evaluated the secretory ability of the pituitary and the elimination of TSH from

a simple kinetic model without using any exogenous TSH. The agreement of the estimated values with other studies supports the validity of the kinetic model and the newly determined values. Normal serum TSH level is a value recently become measurable by immunoradiometric assay. In this study, it was $1.43\pm0.72\,\mu\mathrm{U/m}l$. Though the range of this value was very narrow compared with the range after TRH ($9.14\pm4.26\,\mu\mathrm{U/m}l$ at 25 min), it was found that TSH_0 represents well the secretory ability of a subject.

ACKNOWLEDGMENTS

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