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Effect of Various Doses of Recombinant Human Thyrotropin on the Thyroid Radioactive Iodine Uptake and Serum Levels of Thyroid Hormones and Thyroglobulin in Normal Subjects

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ABSTRACT

Recombinant human TSH (rhTSH), usually given as 0.9-mg doses im on 2 successive days, increases serum thyroglobulin (Tg) and radioactive iodine uptake (RAIU) in residual thyroid tissue in patients with thyroid cancer. We previously reported that a single, relatively low dose of rhTSH (0.1 mg im) is a potent stimulator of T_4, T_3, and Tg secretion in normal subjects. The present study describes the effects of higher doses of rhTSH on thyroid hormone and Tg secretion. Six normal subjects for each dose group, having no evidence of thyroid disease, received either 0.3 or 0.9 mg rhTSH by im injection. Serum TSH, T_4, T_3, and Tg concentrations were measured at 2, 4, and 8 h and 1, 2, 3, 4, and 7 days after rhTSH administration. The peak serum TSH concentrations were 82 ± 18 and 277 ± 89 mU/L, respectively, for the 0.3- and 0.9-mg doses of rhTSH. Serum T_4, T_3, and Tg concentrations increased significantly in subjects receiving 0.3 and 0.9 mg rhTSH, with significant increases in T_4 and T_3 being observed before significant increases in serum Tg. Peak concentrations of serum T_4, T_3, and Tg, after 0.3 mg rhTSH administration, were 100 ± 19, 131 ± 14, and 1035 ± 724% above individual baselines, respectively. Similarly, peak concentrations of serum T_4, T_3, and Tg, after 0.9 mg rhTSH administration, were 102 ± 16, 134 ± 7, and 1890 ± 768% above individual baselines, respectively. These data, compared with previously reported data for the responses to 0.1 mg rhTSH, indicated that 0.1, 0.3, and 0.9 mg rhTSH had similar quantitative stimulatory effects on thyroid hormone and Tg secretion, except that the T_4 response was greater in groups receiving 0.3 and 0.9 mg rhTSH than in the group receiving 0.1 mg rhTSH. We also studied the effect of rhTSH on the thyroid RAIU in the group that received 0.9 mg rhTSH. The 6- and 24-h RAIU values were significantly higher after rhTSH (pre-rhTSH, 6-h value = 12.5 ± 1.8%; 24 h value = 23 ± 2.7%; post-rhTSH, 6 h value = 27 ± 4.8%; 24-h value = 41 ± 4.2%). The stimulating effects of 0.9 mg rhTSH on the 6- and 24-h RAIUs were similar. rhTSH is a potent stimulator of T_4, T_3, and Tg secretion and the RAIU in normal subjects. Single doses greater than 0.1–0.3 mg do not seem to further enhance thyroid hormone or Tg secretion. (*J Clin Endocrinol Metab* **86:** 1660–1664, 2001)

TSH IS THE preeminent thyroid-regulating hormone. Experimental work indicates that it acts through a plasma membrane receptor to stimulate iodide uptake and organification, coupling of thyroglobulin (Tg)-associated iodotyrosines, Tg resorption, and Tg and thyroid hormone secretion (1, 2). In 1998, recombinant human TSH (rhTSH), in the form of Thyrogen (Genzyme Transgenics Corp., Cambridge, MA), was approved by the Food and Drug Administration for use in the management of patients with epithelial cell thyroid carcinomas. Premarketing (phase I/II and phase III) studies in 375 patients with these disorders indicated that rhTSH increased serum Tg secretion from postthyroidectomy remnants and metastatic tumors and stimulated iodide uptake within remnants and metastatic lesions (3–5). In contrast to these more extensive studies in thyroidectomized patients, there is little information concerning the effects of rhTSH in subjects with intact thyroid glands. We have suggested that rhTSH might also be of value in stimulating the thyroid radioactive iodine uptake (RAIU) in iodine-exposed patients and in patients with toxic and nontoxic goiter whose thyroid RAIUs are not elevated and who require definitive ^{131}I therapy. We have also reported that a single dose of 0.1 mg rhTSH, lower than the dose employed in thyroid cancer patients, was a potent stimulus for the release of T_4, T_3, and Tg in normal volunteers (6). The present study was carried out to determine the effects of single higher doses of rhTSH on T_4, T_3, and Tg secretion and on the thyroid RAIU.

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Subjects and Methods

Men and women who did not have evidence of thyroid disease and were between the ages of 20 and 56 participated in the study. After informed consent, a complete history and general physical examination were performed. In addition, initial thyroid function studies, a pregnancy test, a complete blood count (CBC), and a general chemistry profile were obtained. Candidates were accepted into the study if they had no thyroid enlargement or nodules, a normal serum free T_4 index and TSH concentration, and negative tests for an-

tithyroid peroxidase and anti-Tg antibodies. A prior history of thyroid disease or extra thyroidal manifestations of Graves' disease disqualified them from the study. Other exclusion criteria were: pregnancy or nursing; significant cardiac, renal, hepatic, or pulmonary disease; recent surgery or trauma; malnutrition; ingestion of medications known to affect thyroid function; alcohol or drug dependence; and previous administration of rhTSH. The above inclusion and exclusion criteria are identical to those applied in our previous study using 0.1 mg rhTSH (6).

Thyrogen (SA, 4.6 mg/U) was generously provided by Genzyme Transgenics Corp. The protocol is presented in Fig. 1. On the day of rhTSH administration, an indwelling catheter was placed via an antecubital vein. Blood was drawn for baseline thyroid function tests. Subsequently, rhTSH (as Thyrogen) was administered im into the deltoid muscle. This was a dose-ranging study using consecutively higher doses. Therefore, subjects were assigned to a given dose in the order of recruitment. The first six subjects received 0.3 mg rhTSH, and the last six subjects received 0.9 mg rhTSH. Blood was drawn from the indwelling catheter for thyroid function tests at 2, 4, and 8 h after rhTSH administration. Blood was then obtained via venipuncture at 1, 2, 3, and 4 days and at 1 week after rhTSH administration. One week after rhTSH, blood was also drawn for a CBC and chemistries. All sera for thyroid function tests were kept at −20 C until assayed for thyroid function tests. The Committee for the Protection of Human Subjects in Research, University of Massachusetts Medical Center, approved the protocol; and written informed consent was obtained from each participant.

Serum T_4, free T_4 index, T_3, and TSH concentrations were measured using the Automated Chemiluminescence system (Ciba Corning, Inc. Diagnostic Corp., Medfield, MA). Serum Tg concentrations and Tg and thyroid peroxidase antibodies were measured by chemiluminescence using DPC Immulite 2000 (DPC Cirrus, Randolph, NJ). Samples from a given assay were run in duplicate. Sera from the previously reported subjects (6) who received 0.1 mg rhTSH were also included in the present assay.

Five subjects had thyroid RAIUs 6 days before the administration of the 0.9-mg dose of rhTSH. In a sixth patient, the RAIU was performed 56 days before 0.9 mg rhTSH was administered. Both at baseline and 24 h after the administration of rhTSH, 11.17–12.32 MBq (302–333 μCi) of ^{123}I were administered to obtain post-rhTSH RAIUs. RAIUs were measured 6 h after ^{123}I administration and were repeated 18 h later to obtain 24-h values.

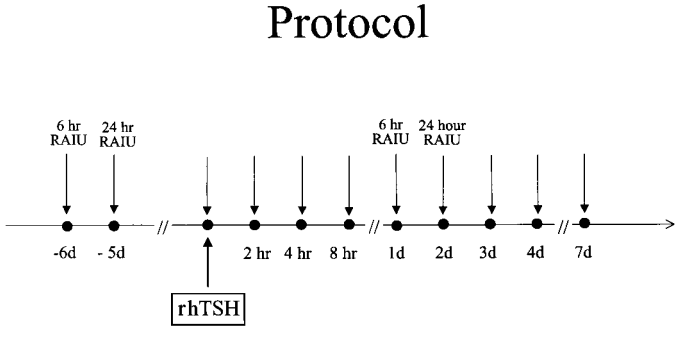

FIG. 1. Protocol for the study. *Arrows*, Times when serum concentrations of TSH, T_4, T_3, and Tg were measured. For the group that received the 0.9-mg dose of rhTSH, the times when RAIU measurements were performed are also shown.

Statistical analysis was performed using data from the initial study in which 0.1 mg rhTSH was administered (assay 1) and from the present study in which 0.3 and 0.9 mg rhTSH were administered (assay 2). All available sera from the study in which 0.1 mg rhTSH was administered were also included in assay 2. ANOVA for mixed models, using restricted estimation by maximum likelihood, was performed. Data from assay 1 and assay 2 were included in the analysis, with the assay number treated as random effect. Log transformation was performed for TSH and Tg. The RAIUs were analyzed using ANOVA for repeated measures. The areas under the curve (AUCs) were determined using the trapezoidal formula (7). The AUCs were compared using ANOVA with multiple-comparison procedures. The SAS Institute, Inc. (Cary, NC) and SPSS, Inc. (Chicago, IL) statistical software programs were used for analysis of all the data. Significance was established at the 95% confidence level. All results are reported as mean ± the SEM, unless otherwise indicated.

Results

Eight women and four men qualified for the study and received either 0.3 or 0.9 mg rhTSH. Their initial laboratory tests, in conjunction with their history and physical examination, were normal and qualified them for the study (Table 1). Subjects tolerated the rhTSH well and reported no significant side effects. The CBC and serum aspartate aminotransferase, alkaline phosphatase, creatinine, and glucose were normal in all subjects 1 week after rhTSH administration.

Serum TSH concentrations increased markedly after administration of either 0.3 or 0.9 mg rhTSH (Fig. 2). Serum TSH concentrations for both groups peaked 4 h after rhTSH injection and were 82 ± 18 mU/L and 277 ± 89 mU/L, respectively. Figure 2 also compares their data with that obtained for the previously reported subjects (6) who received the lower 0.1-mg rhTSH dose. In the group that received 0.1 mg rhTSH, maximal serum TSH concentrations were also reached 4 h after rhTSH administration. The total rhTSH levels available to stimulate the thyroid in the three groups

TABLE 1. Qualifying data for study subjects

	rhTSH, 0.3 mg	rhTSH, 0.9 mg
Men	3	1
Women	3	5
Age, yr	32.7 ± 1.62	40 ± 1.53
TSH, mU/L	1.3 ± 0.36	1.88 ± 0.36
T4, nmol/L	100.4 ± 6.18	95.2 ± 7.46
T_3, nmol/L	1.80 ± 0.12	2.12 ± 0.18
Tg μg/L	12 ± 2.2	9.06 ± 1.7
Hemoglobin, mmol/L	8.44 ± 0.35	7.7 ± 0.24
Hematocrit, %	40 ± 1.61	38 ± 1.42
WBC × 10^9/L	6.1 ± 0.6	6.5 ± 0.51
AST, μkat/L	0.33 ± 0.08	0.3 ± 0.01
Alkaline phosphatase, μkat/L	1.1 ± 0.12	0.87 ± 0.04
Creatinine, μmol/L	73.4 ± 6.2	72.5 ± 1.77
Glucose, mmol/L	5.67 ± 0.63	4.89 ± 0.54

WBC, White blood cells; AST, asparate aminotransferase.

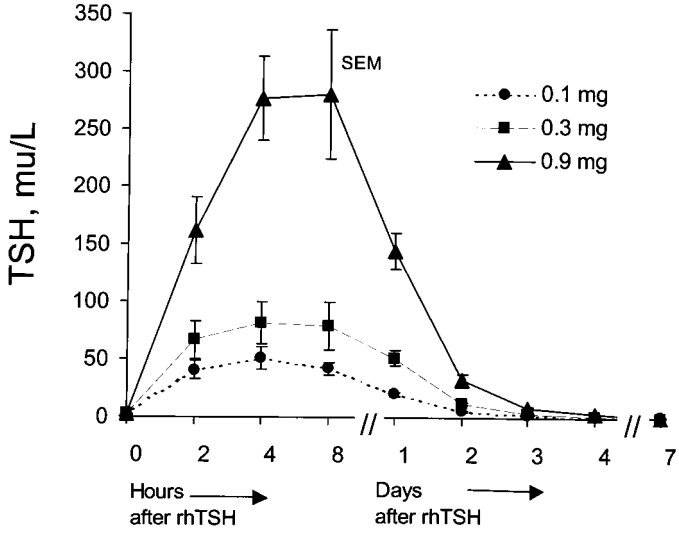

FIG. 2. Serum TSH concentrations in subjects receiving rhTSH. The administered doses of rhTSH are presented *to the right* of the data. The data for the subjects receiving 0.1 mg rhTSH have previously been reported (6) and are shown for comparison.

were estimated from the AUC for serum TSH concentrations (AUC). The mean value for the group receiving 0.9 mg rhTSH was 300% ($P < 0.01$) of the value for the group receiving 0.3 mg rhTSH and was 436% ($P < 0.01$) of the value for the group that received 0.1 mg rhTSH.

Serum T_4 concentrations increased significantly after administration of either 0.3 or 0.9 mg rhTSH (Fig. 3). Maximal serum T_4 concentrations were reached 1 to 2 days after rhTSH administration and were similar (195 ± 11.6 nmol/L after 0.3 mg rhTSH and 189 ± 15 nmol/L after 0.9 mg rhTSH). These data were also compared with that obtained for the previously reported group (6) that received the lower 0.1-mg rhTSH dose. In this group, peak mean serum T_4 concentrations were also achieved 1 to 2 days after rhTSH administration. This value (144 ± 9.78 nmol/L) was significantly lower than the peak values after 0.3 mg rhTSH and 0.9 mg rhTSH ($P < 0.05$).

Serum T_3 concentrations increased significantly after administration of either 0.3 or 0.9 mg rhTSH (Fig. 4). They peaked 1 to 2 days after rhTSH administration and were similar. They were 4.25 ± 0.18 nmol/L after 0.3 mg rhTSH and 4.22 ± 0.09 nmol/L after 0.9 mg rhTSH. These data were also compared with that obtained for the previously reported group (6) that received the lower 0.1-mg rhTSH dose. In this group, peak mean serum T_3 concentrations were achieved 1 day after rhTSH administration. Although the mean value (3.04 ± 0.3 nmol/L) for peak serum T_3 concentrations after 0.1 mg rhTSH was somewhat lower than the mean values for the peak serum T_3 concentrations after 0.3 and 0.9 mg rhTSH, the differences were not significant.

Serum Tg concentrations were unchanged 2, 4, and 8 h after rhTSH administration but were significantly increased 24 h after administration of either 0.3 or 0.9 mg rhTSH (Fig. 5). Maximal serum Tg concentrations were observed 2 days after rhTSH administration and were similar, 84 ± 29 and 99 ± 21 μg/L, for the groups receiving 0.3 and 0.9 mg rhTSH, respectively. These data were also compared with that obtained for the previously reported group (6) that received the lower 0.1-mg rhTSH dose. With this dose, an increase in serum Tg was also observed 1 day after rhTSH administration, and maximal serum Tg concentrations were reached 2 days after rhTSH administration. The peak Tg response, after 0.1 mg rhTSH, was 44 ± 7.6 μg/L, a value which was lower (but not significantly so) than values reached after 0.3 and 0.9 mg rhTSH.

The RAIU was measured before and after rhTSH in every patient who received the 0.9-mg dose. In every patient, the RAIUs were from 22–300% higher after rhTSH. Overall, RAIU values approximately doubled after administration of 0.9 mg rhTSH (Fig. 6). Before rhTSH administration, the

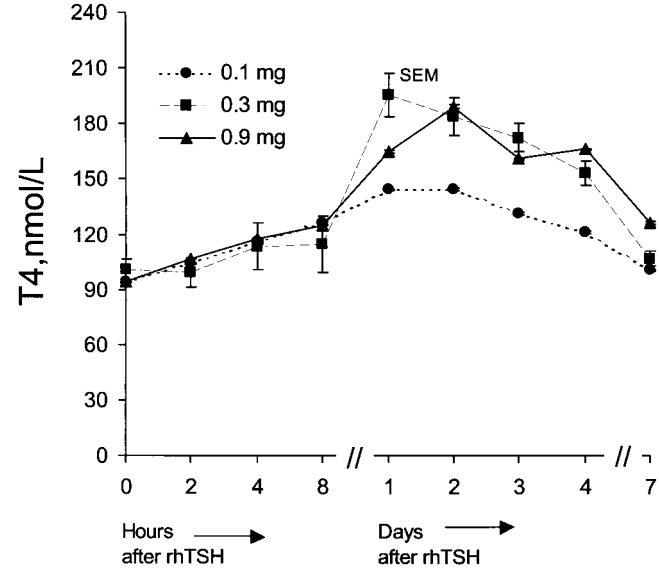

FIG. 3. Serum T_4 concentrations in subjects receiving rhTSH. The administered doses of rhTSH are presented *to the left* of the data. The data for the subjects receiving 0.1 mg rhTSH have previously been reported (6) and are shown for comparison.

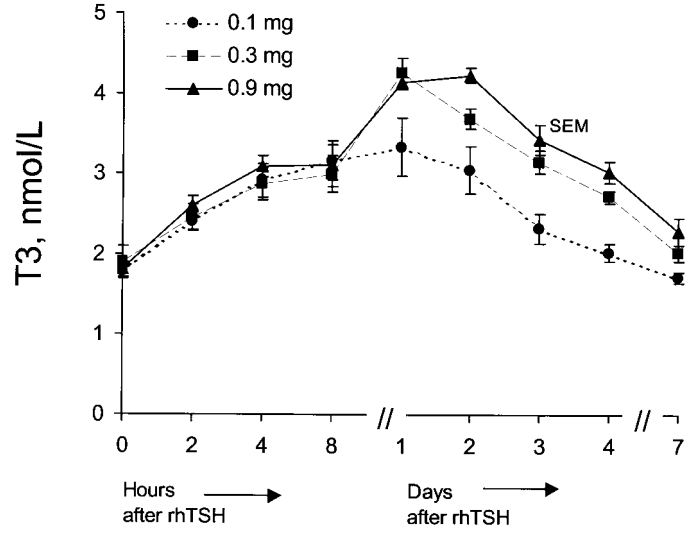

FIG. 4. Serum T_3 concentrations in subjects receiving rhTSH. The administered doses of rhTSH are presented *to the left* of the data. The data for the subjects receiving 0.1 mg rhTSH have previously been reported (6) and are shown for comparison.

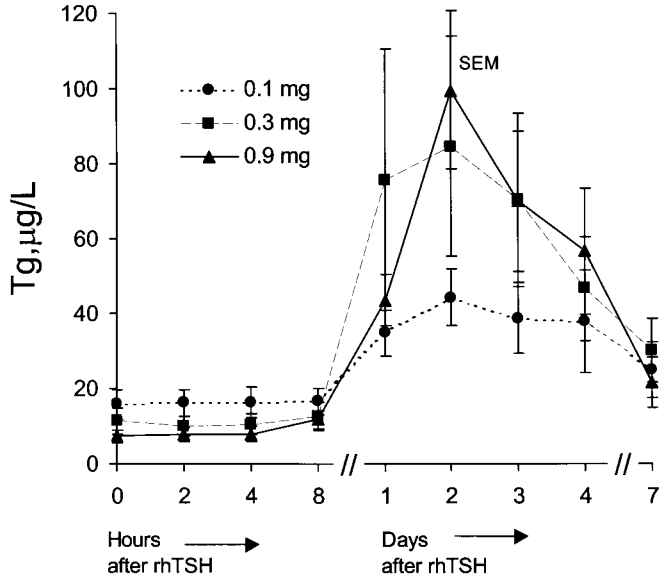

FIG. 5. Serum Tg concentrations in subjects receiving rhTSH. The administered doses of rhTSH are presented *to the left* of the data. The data for the subjects receiving 0.1 mg rhTSH have previously been reported (6) and are shown for comparison.

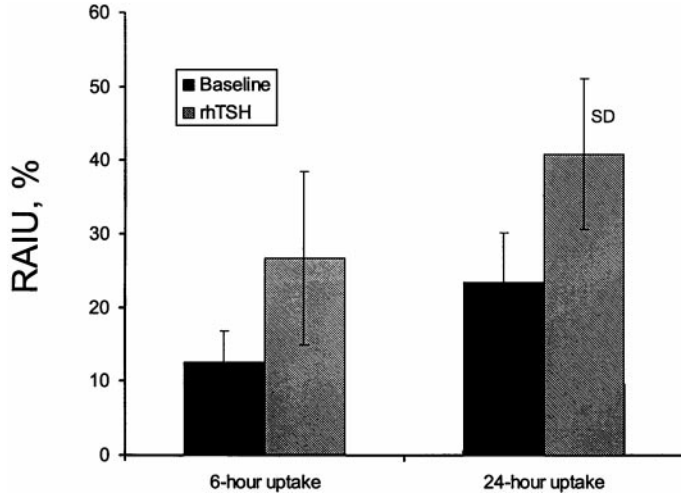

FIG. 6. RAIU values in subjects before and after receiving 0.9 mg rhTSH. Note that the SDs rather than the SEMs are displayed.

mean RAIU values were (mean ± SD) 12.5 ± 4.3% at 6 h and 23.4 ± 6.7% at 24 h. After rhTSH administration, the RAIU values were significantly increased: 26.7 ± 11.8% at 6 h and 40.9 ± 10.2% at 24 h ($P < 0.02$). The increase in the 6-h RAIU was similar to the increase in the 24-h RAIU.

Discussion

The effects of TSH on thyroid hormone secretion, Tg secretion, and thyroid RAIU have been the subject of many studies in humans. Initially, bovine TSH (bTSH) was used for this work (8–11), yielding results that were applied to the diagnosis and differential diagnosis of hypothyroidism, to enhance thyroid scans, and to facilitate 131-I-induced thyroid ablation (12–14). Because bTSH caused allergic reactions and induced TSH antibodies, it is no longer employed in clinical research or practice (15–19). The recent availability of rhTSH has also contributed to the abandonment of bTSH. To date, however, studies (3–5) of rhTSH have been concerned with its ability to stimulate Tg release and thyroid radioiodine uptake in postsurgical thyroid remnants or thyroid cancer metastases. Thus, the only clinical application for rhTSH that has been approved by the Food and Drug Administration is for management of patients with epithelial cell thyroid cancer.

We previously reported the effects of a single relatively low dose of 0.1 mg rhTSH on T_4, T_3, and Tg secretion in subjects with intact thyroid glands and normal baseline thyroid function (6). The present study describes the effects of two higher doses of rhTSH on thyroid hormone and Tg secretion in normal humans, and it presents data on the effects of rhTSH on the thyroid RAIU. The two doses, 0.3 and 0.9 mg, employed for this study are still less than those used in the most comprehensive studies of thyroid cancer patients. In those studies, two or three injections of 0.9 mg rhTSH were administered (4, 5).

The present study and our initial report (6) provide information regarding the relationship between the dose of rhTSH and its effects on thyroid hormone and Tg secretion. The mean serum concentrations of T_4, T_3, and Tg that were achieved after the 0.3-mg dose of rhTSH were somewhat higher than after 0.1 mg rhTSH, but the difference was significant only for serum T_4. A dose of 0.9 mg rhTSH was no more effective in stimulating T_4, T_3, and Tg secretion than was 0.3 mg rhTSH. If the response were proportional to the occupancy of the TSH receptors, the data would be consistent with the concept that TSH receptors become saturated at serum TSH concentrations between 51 and 82 mU/L. These were the peak mean concentrations of TSH achieved when 0.1 and 0.3 mg rhTSH, respectively, were administered.

Previous dose-response studies of the TSH effects on normal thyroid function are limited. Uller *et al.* (20) compared the effects of 0.4 U, 2.0 U, and 10.0 U bTSH, given as Thytropar (Armour Pharmaceutical Company), on serum T_4, T_3, and Tg concentrations. In their studies, the increases in serum T_4 were 15, 42, and 77% (respectively) for the 0.4-, 2.0-, and 10.0-U doses of bTSH. In the present study, the increases in serum T_4 were 55, 100, and 102% (respectively) for the 0 .5- (0.1-mg), 1.4- (0.3-mg), and 4.1-U (0.9-mg) doses of rhTSH. Similarly, the increases in serum T_3 concentrations were 49, 74, and 108% for the 0.4-, 2.0-, and 10.0-U doses of bTSH and were 97, 131, and 134% for the 0.5-, 1.4-, and 4.1-U doses of rhTSH, respectively. Finally, the increases in serum Tg were 36, 109, and 376% for the 0.4-, 2.0-, and 10.0-U doses of bTSH and 210, 1035, and 1890% for the 0.5-, 1.4-, and 4.1-U doses of rhTSH, respectively. In early studies by Schneider *et al.* (21), no difference between the potency of crude bTSH and human cadaveric TSH on the 2- and 3-h thyroid RAIU was observed. Comparison of the data of Uller *et al.* (20) with the present study, however, suggests that the half-maximal dose for the stimulation of T_4, T_3, and Tg secretion in humans is less for rhTSH than for bTSH. This is consistent with the notion that rhTSH is more potent than bTSH in stimulating thyroid hormone and Tg secretion.

Uller *et al.* (22) also compared the effects of bTSH with those of endogenous TSH after TRH administration in nor-

mal human subjects. They reported that after bTSH administration, peak serum T_3 or T_4 occurred earlier than peak serum Tg concentrations. In contrast, after TRH injection, peak serum Tg concentrations occurred early and at the same time as peak serum T_3 and T_4 concentrations. In later studies employing a range of bTSH doses, they observed that the peak serum Tg response to bTSH was delayed, compared with the peak serum T_4 or T_3 responses (20). These reports suggested, therefore, that there may be qualitative differences in the Tg response of the human thyroid to bTSH, compared with endogenous human TSH. In more recent studies (23, 24), however, the serum Tg response to oral TRH administration was delayed, compared with the serum T_4 and T_3 response. In the present study and our initial report (6), the serum Tg response to rhTSH was also consistently later than the serum T_4 and T_3 response. Thus the qualitative effects of bTSH and endogenous TSH on the human thyroid are probably similar.

The present study is one of the first to report the effects of rhTSH administration on the thyroid RAIU in normal subjects. rhTSH administered in a relatively large dose increased the thyroid RAIU by approximately 100%. This response is perhaps slightly less than that reported for bTSH more than 3 decades ago (8, 11). Recently, Huysmans *et al.* (25) presented data indicating that doses of rhTSH as low as 0.01 mg increase the RAIU in patients with nontoxic multinodular goiter residing in an area of mild iodine deficiency. This report and the present study support the potential for rhTSH as an agent to test global thyroid reserve and the function of regions of the thyroid gland, as well as to increase the RAIU when there are clinical indications to do so.

Acknowledgments

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