Significance of Serum Thyrotropin and Plasma Dopamine Concentration in the Regulation of Thyroid Function in Elderly Subjects

TORU MORI1,2), TOSHIHIKO YOKOTA1), TAKASHI AKAMIZU1), DAISUKE INOUE1), MASUMI MIYAMOTO1), SHINJI KOSUGI1), KAZUYOSHI NISHINO1), HIDEO SUGAWA1), HIROTOSHI NAKAMURA1) MASAAKI NAMIKAWA3) AND HIROO IMURA1)

Second Division of Internal Medicine1) and Clinical Molecular Biology2), Kyoto University School of Medicine, Kyoto 606, Japan
Department of Medicine and Geriatrics3), Kyoto Katsura Hospital, Kyoto, Japan

Abstract

In our previous study, we observed a tendency towards an age-related increase in the serum thyrotropin (TSH) concentration. Regulatory mechanisms of TSH secretion in elderly subjects were studied. In 43 elderly subjects, serum TSH did not correlate significantly with serum T4, T3 free T4 or rT3. Further, those with increased TSH (>5 mU/l, 9 subjects) did not overlap with those with low T3 (<0.92 nmol/1, 8 subjects). Increases in serum TSH were not associated with the presence of circulating anti-thyroid autoantibodies.

A TRH test using a 500 µg single bolus injection was performed in 15 subjects. TSH response (basal: 1.92±1.42 (s. d.) mU/1, peak: 11.25±5.33 mU/1, peak: 11.25±5.33 mU/1, respectively) did not differ significantly from that of younger subjects. T3 response after TRH varied greatly and a close correlation was observed between basal T3 and peak T3 (r=0.86), and also between peak T3 and ΔT3 (r=0.81). A significant correlation was observed between ΔTSH and basal T3 (r=0.60). Neither plasma cortisol, epinephrine nor norepinephrine concentrations showed any significant correlation with basal and TRH-stimulated TSH or T3 concentrations. However, the plasma dopamine concentration correlated significantly with ΔTSH (r=0.60) and basal T3 (r=0.52), respectively.

In conclusion, the increase in serum TSH observed in elderly subjects was felt to represent a physiological adaptation to maintain serum T3. Low T3 subjects appear to have a disturbance in this mechanism, with decreased TSH and T3 response to TRH stimulation. The details of this disturbance have not been clarified, but a possible dopaminergic mechanism was suggested by the decreased plasma dopamine concentration observed in the low T3 group.
An age-related decrease in the serum 3, 5, 3'-triiodothyronine (T₃) concentration has been regarded as a possible factor in the process of aging and the development of senile dementia (Levy 1962, Klug & Adelman 1979, Nishikawa et al., 1984). In order to better clarify the role of T₃ in certain pathological manifestations of aging, we recently studied the effect of low dose T₃ administration on elderly subjects (unpublished observation). Through this study, we observed a large percentage (22%) of elderly subjects with increased serum TSH. The mechanism and significance of this TSH increase in elderly subjects is unknown. There have been quite a few reports on the serum TSH concentration and its significance in elderly subjects; however, no conclusive evidence has been demonstrated until now (Lemarchand-Beraud and Vennoti 1969, Mayberry et al., 1971, Bonnyns et al., 1972, Ohara et al., 1974, Cuttelod et al., 1974, Wenzel et al., 1974, Tunbridge et al., 1977, Sawin et al., 1979, Sowers et al., 1982, Harman et al., 1984).

The present study deals with the analysis of increased serum TSH in elderly subjects in relation to various factors which have been known to affect TSH secretion, and demonstrates a disturbance in the regulation of thyroid function in elderly subjects, especially in those with low serum T₃.

### Materials and Methods

Forty-three elderly subjects (80.9±7.8 y. o.) in an institution for aged people were studied. They were exactly the same subjects used for the previous study to see the effect of low dose T₃ administration (unpublished observation). Twenty-one of them received a 25 µg daily dose of L-T₃ (Thyronamin, Takeda, Osaka) for 4 weeks, while the rest received a placebo. Venous blood sampling was performed at 8:00 a.m. after an overnight fast at 0, 2 and 4 weeks of the study.

TRH tests were performed separately in 15 elderly subjects in the same institute. Before and 30, 60, 120 and 180 min after a bolus i.v. injection of 500 µg TRH tartrate (Hirutonin, Takeda, Osaka), venous blood sampling was carried out.

Measurement of T₃, thyroxine (T₄), 3,3', 5'-triiodothyronine (rT₃) and free thyroxine (fT₄) was performed with commercially available radioassay kits. Serum TSH was assayed with a sensitive immunoradiometric assay kit (TSH RIA BEAD II, Dainabot Laboratories, Tokyo) which had a minimum detectability of 0.025 mU/l and a normal range of 0.30 to 5.0 mU/l, respectively (Mori et al., 1986). \( \Delta TSH \) was calculated from the sum of net TSH increases at 30, 60, 120 and 180 min after TRH administration. \( \Delta T₃ \) was the maximal fractional increase in T₃ calculated by subtracting basal T₃ from peak T₃. Autoantibodies to thyroglobulin (anti-Tg) and thyroid microsomes (anti-M) were measured by the passive hemagglutination method (Fujizoki, Tokyo) and titers of more than 1 to 80 dilution were regarded as positive. Plasma cortisol, dopamine, epinephrine and norepinephrine concentrations were kindly measured by Special Reference Laboratories Inc. (Tokyo) by RIA and liquid chromatography.

For statistical analysis the Student’s t-test was used.

### Results

The serum TSH concentration of these 43 elderly subjects did not correlate significantly with serum T₄, T₃, fT₄, rT₃ and their ratios (T₃/rT₃ and rT₃/T₄), and high TSH subjects (\( >5 \) mU/l, 9 subjects) did not overlap with those with low T₃ (\(<0.92 \) nmol/l, 8 subjects). Further, per os T₃ administration for 4 weeks effectively suppressed the serum TSH concentration, and those with high TSH before T₃ administration were not more resistant to T₃ than the others (Fig. 1). Anti-Tg and Anti-M antibodies were positive in 8.6% and 14.3% of the study population, respectively. However, none of the high TSH subjects had detectable antibodies. Some antibody positive subjects had a low T₄ or T₃, but this was not
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Fig. 1. Relationship between serum TSH concentrations before and after T₃ administration. Open circles stand for values obtained 2 weeks and closed circles 4 weeks after T₃ administration. Overall correlation coefficient in subjects was +0.31 (p<0.05), but those at 2 and 4 weeks (+0.30, +0.38, respectively) were not significant at 5% levels.

TRH tests using a 500 µg bolus injection were performed in 15 elderly subjects. Fig. 2 shows the serum TSH and T₃ concentrations before and after TRH. All subjects responded to TRH with a significant increase in both TSH and T₃. The TSH response to TRH was delayed in many subjects, with peak TSH values at 30, 60 and 120 minutes after TRH in 5, 8 and 2 subjects, respectively.

In most subjects studied, the T₃ response was also good. However, there were some poor T₃ responders and they were associated with low basal T₃. As reported previously (Ishihara et al., 1983), healthy young subjects had T₃ response exceeding 0.30 nmol/l after TRH administration. In 5 subjects in the present study, T₃ response was less than 0.30 nmol/l. In addition, 6 of the 15 subjects had a peak T₃ concentration 120 minutes after TRH and a slight fall in T₃ was seen by 180 minutes.

Table 1 summarizes the correlations among various TRH test results and the cortisol and catecholamine concentrations. Basal TSH correlated significantly with peak TSH. An excellent correlation was observed between peak TSH and ∑TSH. Excellent correlations were observed between basal T₃ and peak T₃ and between peak T₃ and ΔT₃. Fig. 3 shows the relationship between the basal T₃ concentration and ∑TSH after TRH. A good correlation was observed.

Fig. 4a shows a significant correlation between the plasma dopamine concentration and ∑TSH after TRH, and Fig. 4b demonstrates another significant correlation between dopamine and basal T₃. Those with high plasma dopamine were found to be good TSH responders to TRH and not to have extremely low basal T₃. On the other hand, subjects with low basal T₃ had low plasma dopamine, reduced pituitary TSH reserve and reduced thyroidal response to TRH-induced TSH.

Discussion

Previous study results of serum TSH in elderly subjects have varied, with reports of either modest or negligible incidence of TSH increase (Lemarchand-Beraud and Vennot 1969, Mayberry et al. 1971, Bonnyns et al., 1972, Ohara et al., 1974, Cuttered et al., 1974, Wenzel et al., 1974, Sawin et al., 1979, Tunbridge et al., 1977). Most previous reports showing increased TSH in elderly subjects attributed it to an association with autoimmune thyroiditis (Bonnyns et al., 1972, Sawin et al., 1979, Tunbridge., et al., 1977) or low fT₄ (Ohara et al., 1974). In the present series, we could not see any significant correlation between
Fig. 2. Serum TSH and T₃ concentrations after TRH injection in 15 elderly subjects.
Open circles stand for male subjects and closed circles for female subjects.

Table 1. Significant correlations obtained comparing TRH test results, plasma cortisol and catecholamine concentrations.

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serum TSH and circulating thyroid hormone or the presence or absence of autoantibodies to thyroid specific antigens. These observations suggested a disturbance in the negative feed-back regulation of TSH, either at the level of the pituitary or CNS. Thyroid hormone unresponsiveness of the pituitary may be considered (Gershengorn and Weintraub 1975), but passive increase in serum T_3 to concentrations mostly within the normal range effectively suppressed serum TSH. Further, a good correlation was observed between serum TSH before and after T_3 administration. Therefore, an abnormality in thyroid hormone feed-back at the pituitary did not appear to be the cause of increased TSH.

In general, the TSH response to TRH in 15 elderly subjects could not be differentiated from that of younger healthy subjects (Mori et al., 1986), except that in
two thirds of the elderly subjects peak TSH was observed later—at 60 or 120 min. Ohara et al. (1974) reported exaggerated TSH response in elderly Japanese subjects, but Harman et al. (1984) observed no abnormal TSH response to TRH infusion in elderly subjects. In spite of good TSH response, the subsequent T₃ increase was not sufficient in all subjects, and 5 of them had a weaker response than 0.30 nmol/l which was the lowest response in young healthy subjects (Ishihara et al., 1983).

Response to exogenous TSH has been variably reported to be either less than normal or unchanged in elderly subjects (Faber et al., 1976, Sartin et al., 1977, Yamada et al., 1984). We observed a close correlation between basal T₃ and peak T₃ and also between peak T₃ and ΔT₃, and a close correlation between basal T₃ and ∑TSH after TRH was also observed. These findings may indicate that increased TSH is effective in maintaining the serum T₃ concentration in elderly subjects.

Among cortisol and catecholamines, only dopamine was found to relate significantly with ∑TSH after TRH and the basal T₃ concentration. The administration of a single dose of dopamine or the dopaminergic agonist, bromocriptine, is known to inhibit TSH secretion (Sowers et al., 1982, Hirvonen et al., 1976, Feek and Toft 1980, Scanlon et al., 1981, Cooper et al., 1983 Ishihara et al., 1985), but chronic administration of pharmacological doses of such agents neither lower the serum TSH concentration nor blunt TSH response after TRH (Hirvonen et al., 1976, Ishihara et al., 1985). Pharmacological doses of norepinephrine have also been reported to exert apparent inhibitory effects on TSH stimulated thyroid hormone release (Ahren 1986, Ahren et al., 1986). To our knowledge, however, there has been no report indicating a regulatory role of physiological levels of catecholamines in regulating pituitary TSH or thyroid functions. The age-related increase in serum TSH together with hyperplasia of TSH secreting cells (Zegarelli-Schmidt et al., 1985) may induce overproduction of dopamine. Such an effect would explain the association of high plasma dopamine with high basal T₃ and high ∑TSH after TRH. On the other hand, decreased urinary excretion of dopamine and dopamine metabolites in Parkinson's disease (Well-Malherbe and Van Buren 1969), Alzheimer type senile demantia and Down's syndrome (Mann et al., 1980) have been reported. Although the significance is not clear, decreased dopaminergic tone may be essential to the development of senile dementia. Decreased dopamine may also diminish the pituitary TSH reserve and further reduce thyroid responsiveness to TRH stimulated TSH, resulting in low serum T₃.

However, before arriving at definite conclusions based on the above findings, it seemed necessary to study a larger number of cases, because the data shown in Figs. 3 and 4 may be affected by the data for one particular patient. In addition, the observed phenomena resemble those associated with malnutrition and severe illness (Wartofsky and Burman 1982). The effects of malnutrition on thyroid functions in elderly subjects should also be considered.

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