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

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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 T_4 , T_3 free T_4 or rT_3 . Further, those with increased TSH (>5 mU/l, 9 subjects) did not overlap with those with low T_3 (<0.92 nmol/l, 8 subjects). Increases in serum TSH were not associated with the presence of circulating anti-thyroid autoantibodies.

A TRH test using a 500 μ g single bolus injection was performed in 15 subjects. TSH response (basal: 1.92 ± 1.42 (s. d.) mU/l, peak: 11.25 ± 5.33 mU/l, Σ : 26.74 ± 12.89 mU/l, respectively) did not differ significantly from that of younger subjects. T_3 response after TRH varied greatly and a close correlation was observed between basal T_3 and peak T_3 ($r=0.86$), and also between peak T_3 and ΔT_3 ($r=0.81$). A significant correlation was observed between Σ TSH and basal T_3 ($r=0.60$). Neither plasma cortisol, epinephrine nor norepinephrine concentrations showed any significant correlation with basal and TRH-stimulated TSH or T_3 concentrations. However, the plasma dopamine concentration correlated significantly with Σ TSH ($r=0.60$) and basal T_3 ($r=0.52$), respectively.

In conclusion, the increase in serum TSH observed in elderly subjects was felt to represent a physiological adaptation to maintain serum T_3 . Low T_3 subjects appear to have a disturbance in this mechanism, with decreased TSH and T_3 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 T_3 group.

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An age-related decrease in the serum 3, 5, 3'-triiodothyronine (T_3) 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 T_3 in certain pathological manifestations of aging, we recently studied the effect of low dose T_3 administration on elderly subjects (unpublished observation).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 T_3 .

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 T_3 administration (unpublished observation). Twenty-one of them received a 25 μ g daily dose of L- T_3 (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 μ g TRH tartrate (Hirutonin, Takeda, Osaka), venous blood sampling was carried out.

Measurement of T_3 , thyroxine (T_4), 3,3', 5'-triiodothyronine (rT_3) and free thyroxine (fT_4) 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). Σ TSH was calculated from the sum of net TSH increases at 30, 60, 120 and 180 min after TRH administration. ΔT_3 was the maximal fractional increase in T_3 calculated by subtracting basal T_3 from peak T_3 . Autoantibody 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 T_4 , T_3 , fT_4 , rT_3 and their ratios (T_3/rT_3 and rT_3/T_4), and high TSH subjects (>5 mU/l, 9 subjects) did not overlap with those with low T_3 (<0.92 nmol/l, 8 subjects). Further, per os T_3 administration for 4 weeks effectively suppressed the serum TSH concentration, and those with high TSH before T_3 administration were not more resistant to T_3 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 T_4 or T_3 , but this was not

Fig. 1. Relationship between serum TSH concentrations before and after T_3 administration.

Open circles stand for values obtained 2 weeks and closed circles 4 weeks after T_3 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.

statistically significant (data not shown).

TRH tests using a 500 μg bolus injection were performed in 15 elderly subjects. Fig. 2 shows the serum TSH and T_3 concentrations before and after TRH. All subjects responded to TRH with a significant increase in both TSH and T_3 . 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 T_3 response was also good. However, there were some poor T_3 responders and they were associated with low basal T_3 . As reported previously (Ishihara *et al.*, 1983), healthy young subjects had T_3 response exceeding 0.30 nmol/l after TRH administration. In 5 subjects in

the present study, T_3 response was less than 0.30 nmol/l. In addition, 6 of the 15 subjects had a peak T_3 concentration 120 minutes after TRH and a slight fall in T_3 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 Σ TSH. Excellent correlations were observed between basal T_3 and peak T_3 and between peak T_3 and ΔT_3 . Fig. 3 shows the relationship between the basal T_3 concentration and Σ TSH after TRH. A good correlation was observed.

Fig. 4a shows a significant correlation between the plasma dopamine concentration and Σ TSH after TRH, and Fig. 4b demonstrates another significant correlation between dopamine and basal T_3 . Those with high plasma dopamine were found to be good TSH responders to TRH and not to have extremely low basal T_3 . On the other hand, subjects with low basal T_3 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 Vennoti 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, Turnbridge, *et al.*, 1977) or low fT_4 (Ohara *et al.*, 1974). In the present series, we could not see any significant correlation between

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

Fig. 3. Relationship between basal T_3 concentration and Σ TSH after TRH administration.

Fig. 4. Relationship between Σ TSH after TRH (a) and basal T_3 concentration (b) with plasma dopamine concentration.

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 T_3 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 T_3 and peak T_3 and also between peak T_3 and ΔT_3 , and a close correlation between basal T_3 and Σ TSH after TRH was also observed. These findings may indicate that increased TSH is effective in maintaining the serum T_3 concentration in elderly subjects.

Among cortisol and catecholamines, only dopamine was found to relate significantly with Σ TSH after TRH and the basal T_3 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 to-

gether 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 T_3 and high Σ 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 dementia 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 T_3 . 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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