TRH-INDUCED TSH AND PROLACTIN RESPONSES IN THE ELDERLY

Summary
Since there are divergencies in the thyrotropin (TSH) response to thyrotropin-releasing hormone (TRH) in old age, and since a hypothalamic-pituitary dysfunction has been suggested in the elderly, we have studied the thyroid function and the TRH responsiveness of TSH and prolactin (PRL) in 56 euthyroid patients over 70 years old, grouped according to age (70-79, 80-89, 90 or more years) and sex. Results were compared to those of 15 postmenopausal women and 11 men. In the elderly patients there was a decrease in plasma tri-iodothyronine (T₃) and an increase in reverse T₃ (rT₃) levels while thyroxine (T₄), basal TSH and PRL levels remained normal. The mean TSH and PRL responses to TRH (250 µg i.v.) were reduced but there was no age effect within the elderly. Only a sex effect was detected, TSH and PRL responses being appreciably lowered in men. In eight patients without severe disease or malnutrition, the response of TSH was not significant. We conclude that despite an apparent euthyroid status, TSH and PRL responses are blunted in elderly patients, and more in men than in women. These data, consistent with a hypothetical hypothalamic-pituitary dysfunction, indicate the difficulties of thyroid status assessment in the elderly.

Thyrotropin-releasing hormone (TRH), the first hypothalamic releasing factor to have its structure determined, has several clinical applications. After intravenous administration of synthetic TRH, there is a rapid release of thyrotropin (TSH) and prolactin (PRL) in normal subjects. This TRH test is a tool of considerable importance widely used for the diagnosis of mild or atypical thyroid disorders and for investigation of the pituitary function [1, 2]. The modulation of pituitary response to TRH by various physiological, pathological or pharmacological effects is well known [1-5]. In the elderly, some studies [1, 6-8] have shown a reduced release of both TSH and PRL, more marked in men than women, whereas normal or increased release were found in other studies [9, 10]. These results have often been based on ill-defined series with a small number of patients.

In view of these diversencies and also the widespread use of the TRH test in old patients who are often suffering from clinically and biologically atypical thyroid disorders, we attempted to establish the limits of criteria for the normal response of TSH and PRL release in a group of very old persons in relation to age and sex.

Simultaneous measurements of TSH and PRL offer a means of providing information on pituitary function and of ascertaining whether the ageing phenomenon

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entails a hypothalamic-pituitary dysfunction, as has been suggested—but not proven [11].

Patients
The population studied was composed of 56 patients aged over 70 years. They were in-patients in a department of internal medicine which has a geriatric orientation. Their mean age was 84.8±1.1 years. Most of the patients were hospitalized in order to evaluate their physical independence and were free from severe acute or chronic disease and of diseases known to alter TSH or PRL response to TRH such as endogenous depression, cirrhosis or renal failure [1, 2]. None of these patients had treatment to modify TSH (corticosteroids or barbiturates) or PRL response (neuroleptics, dopaminergic drugs, etc.). All were clinically euthyroid and none had a history of thyroid disease. When necessary, confirmation of normal thyroid status was obtained by additional tests such as thyroid scintigraphy. Autonomous multinodular goitre was excluded by the same investigation in each patient with insufficient TSH response to TRH.

These patients were divided according to age and sex into six groups with the following characteristics: groups I, II and III consisted of men aged 70-79 years (n=8), 80-89 years (n=8) and 90 years and over (n=8); the women were divided into groups IV, V and VI, respectively: 70-79 years (n=12); 80-89 years (n=8) and 90 and over (n=12). The mean age of these different groups was comparable for both sexes.

This population was compared with control subjects with no history or evidence of thyroid disease. None had severe illness or was taking any treatment known to interfere with thyroid or pituitary function. There were 15 postmenopausal women (aged 52.5±1.5 years) and 11 men (aged 49.0±3.5 years). All the subjects gave informed consent for this investigation.

Methods
A TRH test was performed in exactly the same way on all subjects after an overnight fast. An indwelling catheter was inserted into an antecubital vein and blood was taken 15 min later in order to determine plasma concentrations of total thyroxine (T₄), free thyroxine (FT₄), free T₃ index (FT₃I), tri-iodothyronine (T₃), reverse T₃ (rT₃) and prolactin (PRL). After the intravenous injection of 250 µg of synthetic TRH, TSH was measured at 30, 60 and 120 min. Additionally, PRL was measured at 30 min and T₃ at 120 min. ΔTSH was defined as the difference between peak and basal TSH, and ΔPRL as the difference between PRL at 30 min and basal PRL. The 'thyroid response' to TSH was assessed from the ratio: ΔT₃/ΔTSH, ΔT₃ being the difference between T₃ at 120 min and the basal level.

The plasma concentrations of the various hormones and free fractions were measured by a radio-immunological method; the range of the normal values was established in our laboratory on a healthy population aged 20—65 years. For each dosage, the kit used, the limits of normality, the mean inter-test variation coefficient (VC), the mean intra-test variation coefficient and the nonspecific binding (NSB) are given. Thyroxine: T₄, RIA PEG Abbott's kit; 5-13 µg/ml; intra VC: 3%, inter VC 3%; NSB 5%. Tri-iodothyronine: T₃, RIA PEG Abbott's kit; 80-220 ng/dl; intra VC: 7%; inter VC: 6%; NSB 5%. Free T₄: Amerlex (Amersham) kit; 8-20 pg/ml; intra VC: 2-5%; inter VC 3-7%; NSB 1.5%. TSH: Abbott's kit; <6 µU/ml; intra VC: 8.3%; inter VC: 9%; NSB: 5%. Reverse T₃: Hypolabo rT₃ kit; 9-35 ng/dl; intra VC: 7%; inter VC: 10%; NSB: 7%.

An evaluation of the fixation capacity of thyroid hormone transport proteins was carried out by the T₃ test and the free T₃ index (FT₃I) was calculated by the product of the T₃ level and the T₃ resin uptake ratio modified Hamolski test; Abbott Triosorb Kit, 22-34%, normality limits; intra VC 5%, inter VC 5.5%. Normal values of FT₃I are in the range 1.4-3.

Statistical methods
Results were expressed by the mean ± standard error of the mean (s.e.m.). The groups were compared by means of a variance analysis and the inter-group differences were localized by Scheffe's method. Correlations were calculated by the analysis of linear regression by the method of least squares.
RESULTS

Comparisons between elderly patients and controls

The elderly patients had a lower T₃ blood concentration (P<0.001) and a higher rT₃ blood concentration (P<0.02) than the controls. T₄, free T₄, and FT₄ I were comparable in both groups (Table).

There was no difference between basal TSH or PRL in elderly patients and controls. However, the TSH release was considerably diminished in the elderly patients at 30 and 60 min in the TRH-test as was TSH (P<0.001). The same was observed for PRL at 30 min and for ΔPRL (Table). The thyroid response to TSH assessed by the ratio ΔT₃/ΔTSH was comparable in both elderly and control subjects.

Positive linear correlations were found between rT₃ and age (r=0.54; P<0.001), TSH and age (r=0.62; P<0.001) and ΔPRL and age (r=0.58; P<0.001) only when patients were globally considered but not in the control group or in the elderly patient groups considered separately.

The kinetic TSH response to TRH was comparable in both groups; it did not appear to be delayed in the elderly subjects.

Effect of age and sex in the elderly

No differences were found between the three age groups of elderly persons with regard to any of the hormonal parameters considered, with the exception of ΔPRL which was significantly diminished in group IV of women over 90 years compared to the other elderly women (P<0.05). Age was not correlated with any of the variables considered in the men or the elderly women.

Two-way variance analysis revealed a significant sex-related effect on TSH concentrations at 30 and 60 min, ΔTSH (P<0.025), PRL 30 min and PRL (P<0.05): all were lower in men compared to the elderly women. Further, there was a significant decrease of T₃ in women as compared to men (P<0.025). Thyroid response was comparable in both sexes.

Analysis of individual values

Free T₄ I values and free T₄ concentrations were within normal limits in all the elderly subjects. T₄ concentration values were very scattered and sometime lowered; none exceeded 150 ng/100 ml (upper normal limit: 220 ng/ml). Basal TSH and PRL concentrations were normal.

ΔTSH values were appreciably lowered in elderly men; they were all below 5 µU/ml, whereas in the male controls they were always higher than 4.8 µU/ml. ΔTSH values were more widely dispersed among women: in 19 cases they were below 5 µU/ml in the elderly women, whereas they were always above 6.5 µU/ml in female controls. The frequency of non-measurable TSH responses must be emphasized: two men and six women had a ΔTSH of ≤1 µU/ml, but this was not apparently age-related (Fig. 1).

PRL values were also low in men compared with women but all responses appeared significant since they were all above 2.8 ng/ml in the men and 2.7 ng/ml in the women (Fig. 2).


<table>
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<th>Control</th>
<th>T&lt;sub&gt;3&lt;/sub&gt; (pg/dl)</th>
<th>T&lt;sub&gt;4&lt;/sub&gt; (pg/ml)</th>
<th>TSH (ng/ml)</th>
<th>ΔTSH</th>
<th>PRL (ng/ml)</th>
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*Values which are significantly different in comparisons between controls and elderly patients.

Table. Values (mean±s.e.m.) obtained in each group.
Fig. 1. Individual values of TSH showing effect of age and sex. ● Controls; * group I, aged 70–79 years; △ group II, aged 80–89 years; and ▲ group III, aged 90 years or more.

Fig. 2. Mean values of PRL response to TRH: effect of age and sex.
DISCUSSION

Our results show that TSH and PRL responses to TRH are blunted in elderly euthyroid persons. This phenomenon is more marked in men than in women. The thyroid function is characterized by lower T₃ and higher rT₃ levels while the thyroid responsiveness to TSH remains unchanged.

The persistence of normal thyroid function during old age has been emphasized by many authors. The decrease of T₃ concentrations noted in our study is more closely related to an alteration in extra-thyroid conversion of T₄ into T₃ than to a disturbance of thyroid hormonal secretion. Various factors such as reduced calorie intake acute and chronic diseases common in the elderly are likely to inhibit this peripheral conversion. Increased reverse T₃ concentration is in a way the mirror image of the decrease in T₃ with which it has been correlated in many studies. Indeed, 5'-mono-desiodase, the enzyme which converts T₄ into T₃, is the same as that which breaks down reverse T₃. The 'low T₃ syndrome' may also be an adjustment designed to conserve energy and to spare visceral proteins essential to the elderly. However, a low T₃ does not seem to affect the thyroid status, as is borne out by the FT₄, FT₃, basal TSH and TSH response to TRH usually found in most low T₃ syndromes investigated in the literature [12].

The effect of age on TSH response to the injection of TRH has been assessed in different ways by several authors. Snyder and Utiger [6] were the first to note a gradual falling of TSH response in three groups of men aged 20-39, 40-59 and 60-79 years, but not in women. Hershmann [1] did not observe any relation between the intensity of TSH response and age but pointed out a decreased response in men compared with women. Most authors, with the exception of Rubenstein et al. [13] have reported such a reduction in ΔTSH as a result of either intravenous [6, 7, 10, 14] or oral [8] administration of TRH, which seems to occur earlier in men than in elderly women.

In our data there is certainly a sex-related effect which is significant not only for TSH response but also for T₃ concentration, although there is no obvious link between these two parameters. The effect of age is more complex to analyse and seems to be of little importance after age 70. There appears to be a sharp cut-off in the endocrine control of the hypothalamo-pituitary-thyroid axis after the age of 65, because the age effect is clear when all the subjects investigated are considered, as is shown by the correlation observed between T₃, ΔTSH and age; despite the fact that our controls were postmenopausal women and men over 45 years of age. The significance of this decrease has not been established. The hypothesis of a gradual involutional process is unacceptable because the average TSH response is comparable for the three age groups investigated in the elderly, both in men and women. Moreover, low responders, whether men or women, cannot be separated from other patients by clinical or hormonal criteria. No coherent explanation may be advanced on the basis of our work or of the literature to account for this lowered response.

Others have found that TSH response to TRH is diminished more in men than in women, irrespective of the age of the patients investigated. This difference is usually ascribed to the stimulating effect of oestrogens on the TSH secretion [1]. In our controls, particularly postmenopausal women, such a response in elderly women
compared with men does not seem to be explained by the secretion of oestrogens alone, because it has been clearly shown that such secretion is considerably diminished, if not completely absent, in very elderly women. In fact, it would seem that oestrogens are only a minor factor in the control of TSH secretion.

According to the literature, basal and post-stimulation PRL levels are normal in elderly subjects [3, 15, 16]. The former finding is confirmed in our study; this is not the case for APRL which was clearly diminished in our elderly subjects. In contrast to the men, the elderly women showed a gradual decrease of APRL which may be secondary to a gradual reduction of the oestrogen secretion, which is important in the control of PRL secretion.

There may be a parallel between the decrease in TSH and PRL release despite the lack of correlation between ΔPRL and ΔTSH. There are other similarities, e.g. dopamine has an inhibiting effect on both hormones and serotonin a stimulating effect [2]. However, the study of neurotransmitters in the course of ageing demonstrates a dopaminergic depletion associated with a serotoninergic depletion [17].

From a practical point of view, our results confirm the difficulty of evaluating thyroid function in the elderly. The suppression of the TSH response to TRH associated with normal concentrations of T₄ or FT₄ and a normal or decreased concentration of T₃ is not sufficient either to diagnose or to justify starting treatment of thyrotoxicosis. Additional investigations such as scintigraphy of the thyroid are necessary when clinical signs are not clear. Similarly, thyroid deficiency of central origin should be diagnosed with great care. These considerations in no way detract from the usefulness of the TRH test, but they show its limitations as a diagnostic tool. They should prompt us to revise our strategies in the investigation of the thyroid in the elderly [18].

REFERENCES


Date accepted 9 October 1986