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Inhibitory Effect of Somatostatin on Abnormal GH Response to TRH in Primary Hypothyroidism

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Summary: Thyrotropin releasing hormone (TRH) does not promote GH secretion in normal subjects but it stimulates GH in a proportion of hypothyroid patients.

In this study the response of GH to thyrotropin releasing hormone (TRH) was evaluated in 21 patients with primary hypothyroidism of different origin: 12 with autoimmune thyroiditis, 3 idiopathic, 3 congenital, 3 iatrogenic. 11 of these patients had never been treated, the others were tested after a drug-free period of at least two weeks. Basal plasma concentration of GH was normal in all patients; after TRH administration, a significant increase in plasma GH was observed in 4 patients. In these responsive patients, somatostatin infusion inhibited the abnormal GH response to TRH. It is suggested that the abnormal GH response to TRH in primary hypothyroidism might be caused by a relative deficiency of somatostatinergic control, which is corrected by exogenous somatostatin administration.

Introduction

Thyrotropin releasing hormone (TRH) stimulates TSH and prolactin release, whereas no appreciable changes in plasma GH concentrations are observed in normal subjects. Nonspecific GH responses to TRH were initially described in acromegaly and gigantism (Irie and Tsushima, 1972), and subsequently reported in several disorders including a number of patients with primary hypothyroidism (Collu et al., 1977; Faggiano et al., 1985).

The mechanism of nonspecific GH response to releasing hormones other than growth hormone releasing hormone (GHRH) has not yet been understood. Two major difficulties have been encountered looking for an explanation for the above phenomenon. First, in no one condition including acromegaly in which the highest prevalence of responders is found, the nonspecific GH response to TRH is constantly present; second, the spectrum of disorders associated with abnormal GH response is extremely heterogeneous, including endocrine diseases (Irie and Tsushima, 1972), chronic renal failure (Gonzales-Barcena et al., 1973), hepatic insufficiency (Zanoboni and Zanoboni-Muciaccia, 1977), and psychiatric illness (Maeda et al., 1975; Maeda et al., 1976).

The influence of somatostatin (SRIF) on TRH-induced GH release has been studied in acromegaly with conflicting results: a failure of somatostatin to suppress TRH-induced GH release was reported by Giustina et al. (1984), whereas an impaired GH response to TRH during somatostatin infusion was observed by Gomez-Pan et al. (1975) in different experimental conditions.

This study was undertaken to further investigate the nonspecific GH response to TRH in hypothyroidism and to learn whether exogenous somatostatin abolishes the abnormal response. In addition, we related the nonspecific GH response to TRH with plasma levels of somatomedin-C that seems to inhibit GH secretion through stimulation of somatostatin release.

Material and Methods

Patients. 21 patients, 19 females and 2 males, aged 25–72 yrs, with primary hypothyroidism diagnosed on the basis of clinical and biochemical data, have been included in this study. The origin of hypothyroidism was: autoimmune thyroiditis (12

cases), idiopathic (3), congenital (3), iatrogenic (3). 11 subjects were studied before the beginning of the replacement therapy. 10 patients treated with L-thyroxine were tested after a drug-free period of at least four weeks.

Methods. All the patients were tested with TRH; the patients showing a nonspecific GH response to TRH underwent to combined test with TRH and SRIF. The tests were performed at 08.30 a.m. after an overnight fast with the subjects recumbent throughout the test period.

TRH test. An indwelling needle was inserted in a forearm vein and, after two control specimens were taken (−30 min, 0 min), 200 μg of thyrotropin releasing hormone (Relefact TRH, Hoechst) were injected as an intravenous bolus. Blood samples were obtained at 10, 20, 30, 45, 60, 90, 120 min thereafter. The GH response to TRH was arbitrarily considered significant when plasma GH levels increased by at least three times versus baseline values, provided the net increment exceeded 5 ng/ml and the pattern of response followed a regular profile.

TRH plus SRIF test. 100 μg of somatostatin were administered at time −10 min as a bolus, followed by 200 additional μg infused over 70 min. At time 0 min, 200 μg of TRH were injected as a bolus. Blood samples were taken at −30, −10, 0, 10, 20, 30, 45, 60, 90, 120 min.

Assays. Plasma concentrations of GH were determined by double antibody radioimmunoassay using a commercial kit (HGH-K 2, Sorin, Saluggia). The normal values for this method are 0−10 ng/ml; the minimum detectable dose is 0.25 ± 0.024 ng/ml. Serum prolactin determination was performed by RIA method (Prolactin Ter Kit, Biodata); normal range for this assay is 5−25 ng/ml for females and 5−15 ng/ml for males. The sensitivity of this method is 0.1 ng/ml. TSH concentration was evaluated by ultrasensitive immunoassay with monoclonal antibodies (Allegro HS-TSH, Nichols Institute Diagnostics). Normal values are 0.6−4.6 μU/ml. Circulating SMC was measured by double antibody RIA method on serum previously acidified with 0.5 N HCl and extracted in octadecasilyl-silica columns (Incstar Corporation). The minimum detectable amount with this method is 2.0 nmol/l; normal values in adults are 9.09−46 nmol/l for men and 11.6−48.4 for women. Free thyroid hormones were separated by chromatographic method using Sephadex LH-20 columns and solid phase radioimmunoassay with double antibody method. Normal values for FT_3 are 2.8−5.8 pg/ml, for FT_4 are 6.3−15.3 pg/ml.

Results

Basal hormone levels. All patients had elevated basal TSH levels, ranging between 8.1 and 187 μU/ml, associated with low FT_4, ranging between 2.24 pg/ml and 5.4 pg/ml. Plasma FT_3 ranged between 1.15 pg/ml and 3.5 pg/ml. Basal GH and PRL levels were within normal range (0.22−6.1 ng/ml and 3.3−16.5 ng/ml, respectively). Plasma SMC levels were significantly lower than in a control group matched for age and sex (mean basal level ± SE: 8.18 ± 1.60 nmol/l in hypothyroid patients; 19.18 ± 5.55 nmol/l in controls; $p < 0.05$).

TRH stimulation test. TRH administration elicited a clear increase in plasma TSH and prolactin; in addition TRH injection was followed by an abnormal increase in plasma GH in 4 out of 21 patients (19%). In these responsive patients, GH increase reached a peak (mean basal level ± SE: 4.17 ± 1.66 ng/ml; mean peak ± SE: 19.02 ± 5.2 ng/ml) and decreased therafter. Basal GH and SMC plasma levels of these patients ranged from 0.3 to 6.1 ng/ml and from 4.09 to 12.45 nmol/l, respectively, and were not significantly different from the values observed in non-responsive patients. The 4 GH responsive subjects had autoimmune thyroiditis; 3 of them had never been treated and 1 had been treated for 4 years.

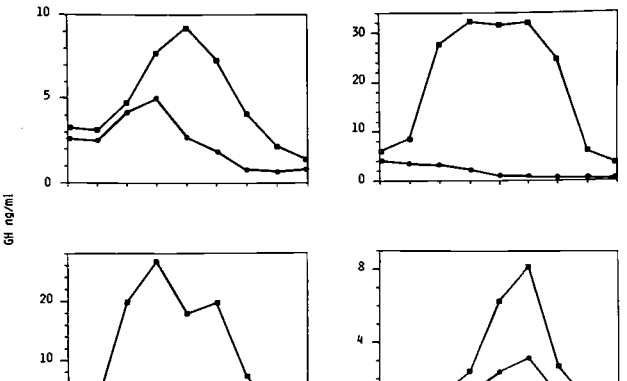

Fig. 1 Plasma GH response to TRH (■−■) and to TRH plus SRIF (●−●) in four patients with primary hypothyroidism. TRH was injected at time 0, and somatostatin was infused between −10 and +60 min

TRH plus SRIF. TRH administration, repeated during somatostatin infusion in the GH responsive patients, failed to induce GH release (mean basal level ± SE: 2.42 ± 0.74 ng/ml; mean peak ± SE: 3.27 ± 0.79 ng/ml). The response of TSH to TRH was reduced by somatostatin infusion (mean peak ± SE: 110.31 ± 13.71 μU/ml after TRH; mean peak ± SE: 82.62 ± 20.60 μU/ml after TRH plus SRIF).

Discussion

Because of the growth defect present in hypothyroidism, growth hormone secretion has been extensively investigated in this condition. Several abnormalities of GH response to different stimuli have been observed in primary hypothyroidism. Reduced responses of GH to insulin tolerance test (ITT) (Brauman and Corvilain, 1968), arginine (Katz et al., 1969) and GHRH (Valcavi et al., 1987; Williams et al., 1985) have been described in patients with untreated disease. Further, abnormal increases of plasma GH following TRH administration have been reported either before or after substitutive therapy (Collu et al., 1977; Faggiano et al., 1985). In the

present study the prevalence of abnormal GH response to TRH was lower (19%) than in previous series of untreated hypothyroid patients (46% and 50%, respectively) (Faggiano et al., 1985; Collu et al., 1977). Somatostatin infusion had an inhibitory effect on TRH-induced GH release in all responsive patients.

The neuroendocrine mechanisms involved in TRH-induced GH release are unclear. In experimental conditions a similar response of GH to TRH can be observed after anatomical disconnection of pituitary, e.g. in hypophysectomized rats with ectopically transplanted pituitaries (Udeschini et al., 1976), or in rats with extensive hypothalamic destruction (Carlson et al., 1973). It has been suggested that in these experimental models the abnormal responsivity of somatotrophs could be caused by a relative deficiency of somatostatinergic control on disconnected pituitary (Scanlon et al., 1979). A decreased content of somatostatin in the hypothalamus has been observed in hypothyroidism in experimental conditions (Berelowitz et al., 1981). The reduced plasma SMC concentration, described in hypothyroidism (Chernausek et al., 1983; Draznin et al., 1980; Furlanetto et al., 1977), clearly evident in the present series, might be related to reduced somatostatinergic tone. In fact, it is known that the negative feedback of SMC on GH secretion is partially mediated via a stimulatory effect of SMC on hypothalamic SRIF release (Berelowitz et al., 1981). The effectiveness of exogenous SRIF in abolishing the abnormal GH responses to TRH observed in this study seems to support the role of relative deficiency of the hypothalamic hormone in promoting the abnormal response of somatotrophs to TRH.

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