Influence of dopaminergic inhibition on serum levels of thyrotrophin and prolactin in patients with hypothyroidism before and after prolonged oral administration of TRH

Harald M. M. Frey and Egil Haug

Medical Department B and Hormone Laboratory, Aker Hospital, Oslo

Abstract. Forty mg TRH/day given orally for 3 weeks to 8 patients with mild primary hypothyroidism decreased serum TSH from a mean of 4.0 ng/ml ± 1.2 (se) to 2.0 ng/ml ± 0.4 (49%), and their mean incremental TSH response to iv TRH was equally reduced from 8.6 ng/ml ± 2.5 to 4.0 ng/ml ± 1.9 (46%). In the same patients serum Prl was 8.2 ng/ml ± 2.2 before oral TRH treatment and 6.6 ng/ml ± 1.5 (81%) after treatment, and the mean incremental Prl response to iv TRH was reduced from 43.5 ng/ml ± 5.0 to 35.9 ng/ml ± 7.5 (83%). The oral administration of 10 mg of the dopamine antagonist metoclopramide increased mean serum TSH from 0.6 ng/ml ± 0.1 (se) to 0.7 ng/ml ± 0.1 (120%) in euthyroid subjects and from 4.0 ng/ml ± 1.2 to 5.7 ng/ml ± 1.6 (145%) in patients with primary hypothyroidism, and mean serum Prl from 8.6 ng/ml ± 0.8 to 109.5 ng/ml ± 24.3 (1251%) and from 8.2 ng/ml ± 2.2 to 119.6 ng/ml ± 45.5 (1460%), respectively. The incremental TSH responses to iv TRH increased 2.3-fold in euthyroid subjects pre-treated with metoclopramide, while no change was observed in the TSH responsiveness in patients with primary hypothyroidism following metoclopramide pre-treatment. In the euthyroid subjects metoclopramide treatment had no effect on the Prl response to iv TRH. In the primary hypothyroid group metoclopramide pre-treatment caused a reduced Prl response to iv TRH in more than 50% of the patients. It is concluded that long-term TRH treatment decreased the serum levels of TSH and Prl as well as the incremental increases in TSH and Prl to iv TRH stimulation in patients with primary hypothyroidism. Long-term TRH treatment did not change the TSH and Prl responses to the dopamine antagonist metoclopramide.

Thyrotrophin (TSH) and prolactin (Prl) secretion from the anterior pituitary gland appear to be under continuous control of hypothalamic and peripheral hormones. The present concept is that thyrotrophin-releasing hormone (TRH) stimulates synthesis and secretion of both TSH and Prl. Dopamine receptors have been demonstrated in the anterior pituitary gland (Brown et al. 1976), and dopamine, which is present in high concentrations in hypothalamus, has an inhibitory role in the control of the secretion of both Prl (Bishop et al. 1972; Refetoff et al. 1974; Takahara et al. 1974) and TSH (Spaulding et al. 1972; Scanlon et al. 1979).

We have previously demonstrated the suppressive effect of long-term oral TRH administration on serum TSH as well as on the TSH response to iv TRH injection (Frey & Haug 1977). In this report we confirm and extend these findings, demonstrating that long-term oral TRH treatment lowers mean basal TSH and Prl as well as the mean incremental TSH and Prl responses to iv TRH in patients with primary hypothyroidism. TRH treatment did not alter the inhibitory effects of dopamine on TSH and Prl secretion.

Materials and Methods

Subjects

Seven female patients and 1 male patient with primary hypothyroidism were studied. They were from 34 to 82 years of age (median = 59), and their body weight ranged from 54 to 98 kg (median = 69). The hypothyroidism was in 1 case post-therapeutic, in 4 cases caused by Hashimoto's thyroiditis and in 3 cases 'idiopathic'. They all received thyroxine medication, and were selected for this investigation because their replacement doses were
insufficient, i.e. they had normal serum \( T_3 \) and \( T_4 \) concentrations and elevated serum TSH levels.

Eight individuals of matching sex, age and weight without thyroid or pituitary disease represented the control group. They went through part of the investigation programme, but did not receive long-term oral treatment with TRH.

**Experimental design**

The patients were fasted overnight. An iv plastic cannula was inserted at 8 a.m. and the patients were kept in bed for 30 min before and during the test. In each case blood was taken for estimation of \( T_3 \), \( T_4 \), TSH and Prl levels immediately before the iv administration of 400 µg TRH. Further blood samples were taken for the measurement of TSH and Prl 30 and 60 min after TRH had been given. In reporting the results the maximal increment in serum concentration at 30 or 60 min after TRH injection was termed \( \Delta \text{max} \) TSH and \( \Delta \text{max} \) Prl. The term 'basal' refers to zero-time concentrations of TSH and Prl.

This standard TRH stimulation test was performed on both the hypothyroid patients and the control subjects on day 0. Two days later both groups were given 10 mg metoclopramide (Prisperan, Nyco, Oslo) orally at 6 a.m., and at 8 a.m. an iv TRH stimulation test was performed as described above.

The hypothyroid patients in addition went through the following procedure: every morning after the combined metoclopramide/TRH-test they received 40 mg TRH (Hoechst) orally for 20 days. On day 21 they underwent a standard TRH stimulation test. On day 22 they received 40 mg TRH orally, and on day 23 another combined metoclopramide/TRH – stimulation test was performed.

**Analyses**

The serum levels of \( T_3 \), \( T_4 \) TSH and Prl were measured by RIA (Aakvaag et al. 1978; Haug et al. 1977; Rutlin et al. 1977; Torjesen et al. 1973). The reference ranges were: \( T_3 \) 1.2–2.5 nmol/l; \( T_4 \) 70–130 nmol/l; TSH (6.6 mU/µg, IRP 68/38) < 1.2 µg/l; Prl (36 mU/µg, IRP 75/504) < 15 (males) and < 20 µg/l (females).

**Statistics**

Significance was tested using the two-sided, non-parametric Wilcoxon test. The results are presented as arithmetic mean values ± se.

**Results**

\( T_3 \) and \( T_4 \)

The hypothyroid subjects studied were under constant \( T_4 \) medication during the study, and there was no significant difference between the results (mean ± se) obtained before (\( T_3 = 1.2 \pm 0.1 \) nmol/l; \( T_4 = 76.0 \pm 3.0 \) nmol/l) they received oral TRH for 21 days and afterwards (\( T_3 = 1.1 \pm 0.1 \) nmol/l; \( T_4 = 75.0 \pm 9.0 \) nmol/l). In the euthyroid subjects the serum concentrations were: \( T_3 = 1.2 \pm 0.1 \) nmol/l and \( T_4 = 103.0 \pm 6.8 \) nmol/l.

**TSH**

The results of the TSH determinations in the euthyroid patients and in the hypothyroid control subjects are illustrated in Fig. 1.

Mean serum TSH levels were 0.6 ng/ml ± 0.1 (se) in the control subjects, and increased to 0.7 ng/ml ± 0.1 (119%) 2 h after oral administration of 10 mg of the dopamine antagonist metoclopramide. In the primary hypothyroid patients mean basal serum TSH was 4.0 ng/ml ± 1.2 before and 5.7 ng/ml ± 1.6 (145%) 2 h after metoclopramide. In the control group treatment with the dopamine-receptor blocking agent caused an increase in serum TSH in 5 of the 9 control subjects, while serum TSH levels were unchanged in 3 subjects and showed a small decline in one subject. In the primary hypothyroid group, metoclopramide treatment increased serum TSH levels in 7 of the 8 patients, while in the 8th patient a decline in serum TSH was observed.

The TSH response to iv TRH, expressed as mean \( \Delta \text{max} \) TSH (see Materials and Methods), was 0.4 ng/ml ± 0.1 before and 1.0 ng/ml ± 0.2 2 h following metoclopramide in the control subjects. All control subjects responded to TRH with an increase in serum TSH and the increments were higher after metoclopramide (\( P < 0.01 \)) than before. In the hypothyroid group mean \( \Delta \text{max} \) TSH after iv TRH amounted to 8.6 ng/ml ± 2.5, as compared to 7.2 ng/ml ± 1.7 when metoclopramide was given 2 h before iv bolus of TRH. The difference between the mean increments in serum TSH is statistically not significant.

Treatment of the 8 primary hypothyroid patients with 40 mg TRH orally for 21 days caused a significant (\( P < 0.05 \)) reduction in serum TSH from 4.0 ng/ml ± 1.2 before TRH to 2.0 ng/ml ± 0.4 (49%) at the end of the TRH treatment period. Administration of metoclopramide to these patients, at the end of the TRH treatment period, had no significant effect on serum TSH (2.4 ng/ml ± 0.6 (125%).

The TSH response to iv TRH, expressed as mean \( \Delta \text{max} \) TSH, was 4.0 ng/ml ± 1.9 (46%) after the treatment with oral TRH as compared to 8.6 ng/ml ± 2.5 before the treatment. This reduction is, however, statistically insignificant because an increased response was observed in one patient (S.A.). All other patients showed substantial de-
Increases in their TSH responses to iv TRH after oral TRH treatment. Deleting patient S.A. from the calculation gives the following results: mean Δmax TSH before oral TRH treatment was 7.7 ng/ml ± 2.7, and following TRH 2.2 ng/ml ± 0.5, a difference that is highly significant (P < 0.001). When the iv TRH tests were performed after metoclopramide treatment, mean Δmax TSH was 5.2 ng/ml ± 2.2 for the entire group, and 3.0 ng/ml ± 0.7 if patient S.A. is left out of the calculations. The mean Δmax TSH after metoclopramide is, thus, significantly (P < 0.01) lower than the corresponding mean Δmax TSH (7.4 ng/ml ± 2.1) obtained before the oral TRH treatment.

**Prl**

The results of the Prl determinations in the control subjects and in the hypothyroid patients are illustrated in Fig. 2.

Mean *serum Prl* concentrations were 8.8 ng/ml ± 0.8 in the control group and 8.2 ng/ml ± 2.2 in the hypothyroid group, and increased to 109.5 ng/ml ± 24.3 (1251%) and 119.6 ng/ml ± 45.5 (1460%) 2 h after oral administration of 10 mg metoclopramide. The increase in Prl after metoclopramide was statistically significant (P < 0.01) in both groups, but there is no difference between the groups.

The Prl response to iv TRH, expressed as mean
Serum levels of Prl (basal prolactin) and incremental Prl responses to iv TRH (Δmax Prl after TRH) in euthyroid subjects (Eu) and in patients with primary hypothyroidism (Hypo). For details see legend to Fig. 1. Mean incremental Prl response to TRH in the group of patients with primary hypothyroidism after deleting one patient (A.L.) who showed an extraordinarily high Prl response. M caused significantly increased basal Prl levels in both euthyroid and hypothyroid subjects, both had no effect on the response to iv TRH.

Δmax Prl (see Materials and Methods), was 45.6 ng/ml ± 15.8 before and 57.5 ng/ml ± 17.4 2 h following metoclopramide in the control group. It is thus noteworthy that the Prl responses to TRH were equal before and after metoclopramide treatment, although treatment with the dopamine antagonist caused a 10-fold increase in serum Prl. In the hypothyroid group mean Δmax Prl after iv TRH was 102.1 ng/ml ± 58.7. This high mean response was, however, due to the extraordinarily great rise in one patient (A.L.): 512 ng/ml. When leaving out this patient from the calculations, the mean in the remaining 7 patients was 43.5 ng/ml ± 4.9, which is not statistically different from the response in the control group. In agreement with the results obtained in the euthyroid subjects, TRH administration resulted in a mean Δmax Prl of 36.3 ng/ml ± 15.0 after metoclopramide. This value is not different from the response obtained before metoclopramide, in despite of the fact that the dopamine antagonist increased serum Prl levels 10-fold.

Treatment of the hypothyroid patients with TRH orally for 21 days had no statistically significant effect on mean serum level of Prl. There was also no difference in the response to iv TRH before and after oral TRH administration for 21 days, and the responses were unaffected by the pre-treatment with metoclopramide (Fig. 2). The statistical evaluation gives the same result whether or not patient A.L. is included (vide supra).

Discussion

As previously demonstrated (Frey & Haug 1977) long-term TRH treatment of patients with primary hypothyroidism leads to a concomitant decrease in
plasma TSH levels (49%) and in incremental TSH responses (46%) to iv TRH. The decreased plasma TSH levels and the impaired TSH responses were not accompanied by an increase in the plasma levels of the thyroid hormones. These results, therefore, probably reflect a direct effect of TRH on the thyrotrophs. Recent studies indicate that the number of plasma membrane receptors for a variety of hormones including TRH (Hinkle & Tashjian 1975; Gershengorn 1978; Nemeroff et al. 1980) can be modulated, and it has been suggested that this may serve as an important site of regulation of hormone action. The decreased plasma TSH levels and the impaired responses to iv TRH could therefore be due to a decrease in the number of available TRH receptors. Thyrotrophs would then be less sensitive to TRH, and spontaneous TSH release as well as the acute release of TSH following iv TRH would decline.

Small decreases in plasma Prl levels (81%) as well as in incremental Prl responses (83%) to iv TRH were observed after the oral TRH treatment period. These decreases were smaller than the corresponding decreases in plasma TSH levels and in incremental TSH responses to iv TRH. The reason for this discrepancy is not known. Most authors have shown a Prl response to TRH equal to or greater than that observed for TSH throughout the entire dose-response spectrum (Bowers & Friesen 1973; Gautvik et al. 1973; Jacobs et al. 1973), although Spencer et al. (1980) have recently reported that a low dose TRH infusion raised serum TSH without influencing serum Prl levels. A different sensitivity of lactotrophs and thyrotrophs to low doses of TRH, however, would not explain the greater reduction in TSH plasma levels and in TSH responsiveness to iv TRH after long-term TRH treatment since relatively high doses of TRH were used in the present study (Bowers & Friesen 1973; Gautvik et al. 1973; Jacobs et al. 1973).

It is evident from this study as well as from other studies that basal Prl levels are not generally elevated in primary hypothyroidism as is TSH, and TRH-stimulated Prl release is not that sensitive to inhibition by thyroid hormones, as TSH release (Snyder et al. 1973). It is, therefore, evident that the thyroid hormones modulate the TRH-mediated Prl release differently from their action on TSH release.

There is considerable evidence to indicate that dopamine has an inhibitory role in the control of TSH and Prl secretion. Dopaminergic receptors have been demonstrated in the anterior pituitary gland of rats (Caron et al. 1978) and cattle (Calabro & MacLeod 1978), and dopamine inhibits both TSH and Prl secretion in isolated rat pituitary cells (Foord et al. 1980; Caron et al. 1978). In agreement with these in vitro studies we found that the dopamine-receptor blocking drug, metoclopramide, caused more than a 10-fold increase in Prl levels in both euthyroid and hypothyroid subjects, while the rise in TSH levels were considerably smaller in both groups. Similar findings have been reported by Scanlon et al. (1979) and Feek et al. (1980), indicating that the inhibitory effects of dopamine are most pronounced on Prl secretion. It is noteworthy that the incremental TSH responses to TRH in euthyroid subjects were doubled after metoclopramide pre-treatment. In subjects with primary hypothyroidism, showing an exaggerated TSH response to iv TRH, however, metoclopramide pre-treatment resulted in no further increase in the TRH-induced TSH responses. It has been reported by others (Scanlon et al. 1979; Feek et al. 1980) that the dopaminergic inhibition of TSH secretion is gradually decreased with increasing hypothyroidism, while the inhibitory effect of dopamine on Prl secretion is almost uninfluenced by thyroid function (Scanlon et al. 1981).

It has been shown that TRH treatment caused a 50% decrease in the concentration of somatostatin receptors on Prl secreting rat pituitary cells in culture (Schonbrunn & Tashjian 1980). The observation that long-term TRH treatment had no effect on the incremental TSH responses to metoclopramide, however, indicates that the TRH treatment did not influence the sensitivity of the thyrotrophs to dopamine inhibition.

Acknowledgments
Financial support from Norwegian Society for Fighting Cancer is gratefully acknowledged. The authors wish to thank Mrs. Kjersti Gunneng for typing the manuscript and Mr. Arne Pedersen for photographic services.

References


Received on February 15th, 1983.