Thyrotrophin and prolactin responses to thyrotrophin-releasing hormone in patients with Parkinson’s disease

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Abstract. The thyrotrophin (TSH) and prolactin (Prl)-releasing effects of TSH-releasing hormone (TRH) were investigated in 20 subjects with Parkinson’s disease (PD), unmedicated, on chronic treatment with a combination levodopa-benserazide (Madopar) or levodopa-carbidopa (Sinemet) or withdrawn from therapy. Administration of TRH (200 μg iv) induced in unmedicated patients TSH and Prl responses significantly lower than those of sex- and age-matched controls. In patients on Madopar therapy the TSH and Prl responses to TRH were greater than in unmedicated patients and comparable to those of controls, while in patients on Sinemet therapy the pituitary responses were undistinguishable from those of unmedicated subjects. Withdrawal of Madopar therapy resulted in a marked diminution of the TSH response but did not affect the Prl response to TRH. Withdrawal of Sinemet therapy did not alter the TSH and Prl responses to TRH. Concomitant evaluation of growth hormone (GH) levels, in none of the subjects evidenced non-specific changes in plasma GH following TRH. Since TSH and Prl responses to TRH are inhibited by an enhancement of the dopaminergic tone, it would appear that the latter is preserved in the tuberoinfundibular system of unmedicated subjects and subjects on chronic Sinemet therapy, but is defective in subjects on chronic Madopar therapy.

The effect of dopamine (DA) stimulation on growth hormone (GH) release has been widely investigated in Parkinson’s disease (PD) also dictated by the concern that drug-induced GH changes may interfere with the therapeutic potential of the DA agonists used (Cotzias et al. 1976a,b).

Less attention has been paid to aspects of dopaminergic control of prolactin (Prl) and thyrotrophin (TSH) secretion. The 24 h mean concentrations and secretion pattern of Prl were normal in untreated PD subjects, and DA agonists, as expected, suppressed Prl secretion (Bell et al. 1977). Similarly, baseline TSH levels and other indices of thyroid function were within a normal range in PD subjects under good control on chronic therapy (McCaul et al. 1974; Wingert & Hershman 1979).

However, few reports have appeared showing that the Prl and TSH responses to thyrotrophin-releasing hormone (TRH) are consistently reduced in PD subjects untreated or under chronic therapy (McCaul et al. 1974; Morgante et al. 1978). This fact has been attributed to a state of hypersensitivity of the hypothalamic DA system to the stimulant action of TRH with ensuing mobilization of DA from neuronal stores and its delivery to the anterior pituitary (Morgante et al. 1978). It must be recalled in this context that drug-induced activation of DA neurotransmission suppresses both the TRH-induced Prl (Besses et al. 1975) and TSH (Spaulding et al. 1972) rise.

The most traditional therapy of PD is based on the use of levodopa combined with peripheral inhibitors of dopa decarboxylase (DDI) i.e. with

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carbidopa (Sinemet) or with benserazide (Madopar). Combined administration of levodopa and DDI by increasing DA availability to the central nervous system (CNS) would enhance CNS-DA neurotransmission (Bartholini & Pletscher 1975). In the present report it seemed worthwhile investigating the TSH- and Prl-releasing effects of TRH in PD subjects unmedicated, on chronic Madopar or Sinemet therapy or withdrawn from therapy. Hopefully, this approach would have provided insight into the mechanism(s) underlying the blunted TSH and Prl responses to TRH of PD subjects. Plasma growth hormone (GH) concentrations were also evaluated after acute TRH testing.

Materials and Methods

In all 28 subjects, 20 patients and 8 controls, were studied. Patients consisted of 16 women and 4 men, aged 30–76 years (mean 56.4 years) with idiopathic PD of 1–15 years duration (mean 6.9 years). Control subjects consisted of 5 women and 3 men, aged 32–53 years (mean 48.0 years). They were in-patients who volunteered for the study, recovered from minor disease, with no family history of diabetes and free of endocrine and metabolic disorders.

Unmedicated patients

Five women, aged 30–62 years (mean 51.0 years) with idiopathic PD of 1–10 years duration (mean 5.7 years).

Patients on therapy

Madopar. Six women and 1 man, aged 42–69 years (mean 55.5 years) with idiopathic PD of 2–15 years duration (mean 7.8 years), who were taking one capsule of Madopar (levodopa 200 mg, benserazide (1-DL-seryl-2-(2-3-4 trihydroxybenzyl) hydrazine hydrochloride 50 mg), 2 to 8 times daily for periods ranging from 1 to 8 years. Three of these subjects (2 women and 1 man) were also studied following Madopar withdrawal.

Sinemet. Five women and 2 men, aged 47–76 years (mean 62.4 years) with idiopathic PD of 5–11 years duration (mean 7.8 years), who were taking one capsule of Sinemet (levodopa 250 mg, carbidopa (l-α-methyl-dopa-hydrazine), 25 mg) 3 to 6 times daily for periods ranging from 1 to 3 years. Four of these subjects (2 women and 2 men) were also studied following Sinemet withdrawal.

Patients withdrawn from therapy

Two women and 2 men, aged 40–55 years (mean 49.3 years) with idiopathic PD of 4–6 years duration (mean 5.0 years) had withdrawn Madopar therapy (see above) 4 days before; 2 women and 2 men, aged 47–68 years (mean 58.0 years) with idiopathic PD of 6–9 years duration (mean 6.5 years) had withdrawn Sinemet therapy 4 days before.

Clinical procedure

All experiments were performed in the morning after an overnight fast and about 12 h after the last drug administration. Informed consent was obtained from each patient. All subjects were supine, comfortable and free of stress during the test. Serial blood specimens were collected through an indwelling polyethylene catheter placed in the antecubital vein and kept open by a slow infusion of saline starting at 08.00–08.30 h. After a 30 min period from placement of the venous catheter, 200 µg TRH (Relefact®, Hoechst, Frankfurt, WG) was administered iv as a bolus and samples were obtained at −30 and 0 min and 30, 45, 60 and 90 min following TRH administration.

Hormone assays

Plasma was obtained by centrifugation and stored at −20°C until assayed for TSH, Prl and GH according to previously described double-antibody radioimmunoassay methods (see Brambilla et al. 1978). The TSH standard was WHO 68/38; the GH and Prl standards were WHO 66/217, 2 µU of which corresponds to 1 mg of human growth hormone and MRC 71/282, 40 µU of which corresponds to 1 ng NIH No. 1, thyroxine (T₄) and triiodothyronine (T₃) were evaluated according to Amerlex T₄ and T₃ RIA kits. Data were expressed as absolute values ± SEM and significance of differences was calculated by Dunnett's t-test (Dunnett 1964).

Results

TSH

Basal TSH levels

TSH levels in plasma of unmedicated PD subjects and subjects on Sinemet therapy were not different from those of control subjects (1.7 ± 0.5, 0.9 ± 0.1 vs 1.0 ± 0.1 µU/ml, respectively). However, plasma TSH levels of patients on Madopar therapy were significantly higher than those of patients on Sinemet therapy and of controls (2.0 ± 0.3 vs 0.9 ± 0.1 and vs 1.0 ± 0.1 µU/ml, P < 0.05, respectively).

TRH-induced TSH rise

Administration of TRH induced a rise in TSH levels in unmedicated subjects which was significantly lower than that present in both control
subjects and patients on chronic Madopar therapy. Peak plasma TSH levels were respectively 6.6 ± 1.3, 16.4 ± 0.5 and 14.0 ± 3.6 μU/ml at 30 min and a significant difference was present between unmedicated subjects and subjects on chronic Madopar therapy at 30 min (P < 0.05) and between the former and controls at 30, 45, 60 and 90 min (P < 0.01) (Fig. 1, left panel). Fig. 1 (right panel) shows the TSH-releasing effect of TRH in patients on Sinemet therapy evaluated in comparison with the response present in controls. It is apparent that in patients receiving Sinemet the TRH-induced TSH rise was significantly lower than in controls: peak plasma TSH levels were respectively 9.2 ± 2.3 and 16.4 ± 0.5 μU/ml at 30 min and a significant difference was present between the two groups at 30, 45, 60 and 90 min (P < 0.05).

Although blunted, at no time-interval the TSH response to TRH present in patients on Sinemet therapy was significantly different from that present in unmedicated PD subjects or in patients under chronic Madopar therapy.

Fig. 2 (left panel) shows the TSH-releasing effect of TRH in patients withdrawn from Madopar therapy evaluated in comparison with the response present in patients on chronic therapy. It is evident that drug withdrawal resulted in a considerable reduction of the TSH response which was evoked by TRH in patients on therapy; a statistically significant difference was attained at 30 and 60 min (5.8 ± 2.7 vs 14.0 ± 3.6 μU/ml, P < 0.05 and 2.5 ± 0.9 vs 9.6 ± 2.3 μU/ml, P < 0.01, respectively).

Fig. 2 (right panel) shows the TSH-releasing effect of TRH in patients withdrawn from Madopar or Sinemet therapy evaluated in comparison...
with the responses present in unmedicated and control subjects. It is apparent that no difference was present in the TSH response to TRH in unmedicated subjects and subjects withdrawn from either therapy; a significant difference was present between the TSH responses of these three groups and that of control subjects (unmedicated and Madopar withdrawal vs controls, $P < 0.01$ at 30, 45, 60 and 90 min; Sinemet withdrawal vs controls $P < 0.05$ at 30, 45, 60 and 90 min).

**TRH-induced Prl rise**

There was no significant difference in basal Prl levels among various groups of PD subjects and between them and control subjects. Administration of TRH induced a rise in Prl levels in unmedicated subjects which was significantly lower than that present in either controls or patients on Madopar therapy. Peak plasma Prl levels were respectively $33.7 \pm 5.7$, $60.8 \pm 6.9$ and $59.0 \pm 11.3$ ng/ml at 30 min and a significant difference was present between unmedicated subjects and patients on Madopar therapy ($P < 0.05$ at 45 min) or controls ($P < 0.05$ at 60 and 90 min) (Fig. 3, left panel).

Fig. 3 (right panel) shows the Prl-releasing effect of TRH in patients on Sinemet therapy evaluated in comparison with the response present in controls. It is evident that in patients the TRH-induced Prl rise was significantly lower than in controls; peak plasma Prl levels were respectively $27.5 \pm 8.7$ and $60.8 \pm 6.9$ ng/ml at 30 min and a significant difference was present between the two groups at this time ($P < 0.05$).

It is noteworthy that the Prl response to TRH present in patients on Sinemet therapy was significantly lower than that present in subjects on Madopar.

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**Fig. 2.**

Left panel: effect of TRH on hTSH levels in patients on or withdrawn from Madopar therapy. ◆ = difference statistically significant vs patients on Madopar therapy. Right panel: effect of TRH on plasma TSH levels in control subjects, unmedicated PD subjects and patients withdrawn from Madopar or Sinemet therapy. For the sake of clarity the symbols denoting differences statistically significant vs control subjects have been omitted (see text for details).
Left panel: effect of TRH on hPRL levels in control subjects, unmedicated PD subjects and patients on Madopar therapy. * = difference statistically significant vs control subjects; • = difference statistically significant vs patients on Madopar therapy. Right panel: effect of TRH on plasma hPRL levels in control subjects and PD patients on Sinemet therapy. * = difference statistically significant vs controls.

Left panel: effect of TRH on hPRL levels in patients on or withdrawn from Madopar therapy. Right panel: effect of TRH on TSH levels in control subjects, unmedicated PD subjects and patients withdrawn from Madopar or Sinemet therapy.
par therapy at 30 min (24.5 ± 8.7 vs 59.0 ± 11.3 ng/ml, P < 0.05).

Fig. 4 (left panel) shows the Prl-releasing effect of TRH in patients withdrawn from Madopar therapy evaluated in comparison with that of patients on chronic therapy. Although lower, at no time interval the Prl response to TRH present in patients withdrawn from Madopar was significantly different from that of patients on chronic therapy. Fig. 4 (right panel) shows the Prl-releasing effect of TRH in patients withdrawn from chronic Madopar or Sinemet therapy evaluated in comparison with those of unmedicated and control subjects. There was no significant difference in the Prl response to TRH between patients withdrawn from Madopar or Sinemet therapy nor between them and controls.

In none of the subjects investigated administration of TRH induced significant changes in baseline GH levels (data not shown) or overt behavioural effects.

$T_4$ and $T_3$ plasma levels

Plasma levels of $T_4$ and $T_3$ (mean of −30 and 0 min values on the day of the experiment) were within normal limits in all experimental groups.

Plasma $T_4$ levels were increased in subjects on Madopar therapy and in subjects withdrawn from Madopar or Sinemet therapy when compared to control values, while no difference was present in $T_3$ levels among experimental groups (Table 1).

**Discussion**

Parkinson’s disease is a neurologic disorder which affects motor function, mainly characterized by degenerative changes of the nigrostriatal dopaminergic neurons. In our study, TRH, a potent TSH and Prl secretagogue in healthy human beings, induced different secretory responses in subjects with idiopathic PD. Baseline TSH levels were normal in unmedicated PD subjects but following TRH stimulation there was only a small rise in plasma TSH. A similar observation has been previously reported in Parkinsonian patients unmedicated or under levodopa therapy, despite the lack of clinical and biochemical signs of thyroid dysfunction (McCaul et al. 1974; Morgante et al. 1978).

The blunted TSH responses to TRH of unmedicated PD subjects contrasted that of patients on Madopar therapy, in whom the TRH-induced TSH rise was significantly greater and similar to that of controls. Differently from patients on Madopar therapy, PD patients who received chronically a regimen of Sinemet had a TSH response to TRH indistinguishable from that of unmedicated subjects. In addition, their basal TSH levels were significantly lower than in patients on Madopar therapy. Wide individual variability and the relative small number of patients did not allow to evidence a difference in the TSH response to TRH between patients receiving Madopar or Sinemet therapy.

**Table 1.**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
<th>$T_4^*$ (µg/100 ml)</th>
<th>$T_3^*$ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td>8</td>
<td>5.93 ± 0.26</td>
<td>0.79 ± 0.05</td>
</tr>
<tr>
<td>Unmedicated subjects</td>
<td>7</td>
<td>6.98 ± 0.45</td>
<td>0.75 ± 0.08</td>
</tr>
<tr>
<td>Madopar therapy</td>
<td>7</td>
<td>7.98 ± 0.6**</td>
<td>0.82 ± 0.06</td>
</tr>
<tr>
<td>Sinemet therapy</td>
<td>6</td>
<td>7.16 ± 0.6</td>
<td>0.87 ± 0.04</td>
</tr>
<tr>
<td>Madopar withdrawal</td>
<td>4</td>
<td>9.35 ± 1.0***</td>
<td>0.87 ± 0.03</td>
</tr>
<tr>
<td>Sinemet withdrawal</td>
<td>5</td>
<td>8.24 ± 0.4**</td>
<td>0.82 ± 0.06</td>
</tr>
</tbody>
</table>

* Normal values: $T_4 = 4.2-11.0$ µg/100 ml; $T_3 = 0.5-1.6$ ng/ml.

** P < 0.05 vs control subjects.

*** P < 0.01 vs control subjects.
Determinations of thyroid hormones evidenced the presence of plasma T4 and T3 within normal limits in all experimental groups with only random increases in plasma T4 in subjects on Madopar therapy and subjects withdrawn from Madopar or Sinemet therapy. This excludes the possibility that the different TSH responses to TRH may have been due to the different feedback action of thyroid hormones on pituitary thyrotrophs and that specific treatments affected thyroid function.

Similarly to our findings, Berger & Kelley (1981) found no statistically significant difference in thyroid function between PD patients on levodopa or Sinemet and age- and sex-matched controls.

Findings hitherto reported for the TSH response are almost duplicated when the Prl response to TRH is considered. In fact, in unmedicated PD subjects the Prl rise after TRH was significantly smaller than in controls but no difference was present between the Prl elevation present in the latter and in subjects on Madopar therapy. In patients on Sinemet therapy the TRH-induced Prl rise was considerably reduced and, in this instance, significantly lower than that present in PD subjects on Madopar therapy.

The reason(s) why the TRH-induced TSH and Prl elevations in patients on Madopar therapy exceed those of unmedicated patients and of patients on Sinemet therapy is not readily apparent. Madopar and Sinemet are a combination of levodopa with benzerazide and carbidopa, respectively, and in view of the mechanism of action of the two DDIs their administration concurrent to that of levodopa should result in greater stimulation of CNS-DA function and hence suppression of the TSH and Prl responses to TRH (see Introduction). It must be recalled, however, that the impenetrability of the blood brain barrier (BBB) by peripheral DDIs is only relative and that these compounds at high doses may cross it (Porter 1971). It is therefore tempting to suggest that benzerazide, but not carbidopa, may penetrate inside the BBB and impede conversion of levodopa to DA in areas located above the median eminence (ME). Alternatively, benzerazide may have a greater inhibitory effect than carbidopa upon peripheral decarboxylase activity and hence may block more effectively DA synthesis at areas lying outside the BBB i.e. ME and/or anterior pituitary, which are crucial for the inhibitory control of DA over TSH and Prl secretion. Experiments are now in progress in our laboratory for ascertaining in different experimental models the mechanism(s) whereby benzerazide and carbidopa affect DA function in the hypothalamo-pituitary system.

Whatever the correct interpretation of the mechanism(s) of action of benzerazide will be the greater TSH and Prl rise of subjects on Madopar therapy may be viewed as the result of TRH acting on thyrotrophs and lactotrophs partially freed from the restrain of DA delivered through the hypophyseal portal circulation. Enhancement or preservation of DA function in the mediobasal hypothalamus as a result of Sinemet administration would result instead in a diminished TSH and Prl response to TRH.

That pituitary responses to TRH in PD subjects do not reflect a random variability but are instead causally related to treatment is implied by some of the experiments of drug withdrawal. In patients withdrawn from Madopar for 4 days the TSH response to TRH was detectably reduced and was indistinguishable from that of unmedicated subjects. This pattern, however, was not duplicated by the Prl response, which was unaltered following Madopar withdrawal. A tentative explanation of these findings is that chronic treatment with Madopar by reducing DA delivery to the lactotrophs, caused an increase of the pituitary pool of Prl, which outlasted the short withdrawal period. In contrast to Madopar, withdrawal of Sinemet did not alter TSH and Prl responses to TRH, a finding in keeping with the similar TRH-induced TSH and Prl elevations of unmedicated and Sinemet-treated patients.

If the extent of TSH and Prl responses to TRH in Parkinsonian patients is a true reflection of DA neural activity in the tuberoinfundibular DA (TIDA) tract, it would appear that in unmedicated patients TIDA function is preserved and even greater than that present in controls. Sinemet, in fact failed to decrease further the TSH and Prl responsiveness to TRH of PD subjects. Alternatively, the lack of the effect of Sinemet may be due to the long interval, (12 h) elapsing between its last administration and starting of TRH experiments. This possibility is currently explored in our laboratory.

Abnormal GH responsiveness to TRH is a hallmark of some endocrine and psychiatric disorders (Müller et al. 1978) and has been attributed to an altered brain monoamine function (Müller et al. 1978). This type of alteration may not be present in the CNS of patients with extrapyramidal disorders,
since in neither subjects with Huntington’s disease (Müller et al. 1979) nor in PD subjects (this study) was TRH competent to induce a rise in plasma GH levels.

In sum, studies conducted in control and PD subjects whether unmedicated or on chronic conventional therapy, did not provide evidence to support the view that in unmedicated patients there is an inherent deficiency of the TIDA function, which may account for an enhanced susceptibility of the DA system to TRH (see Introduction). In addition, in none of our patients was TRH administration followed by symptoms (improvement in well-being, enhanced clarity of thought, etc.) which may be attributed to a primary CNS locus of action of the peptide (Kastin et al. 1972).

Chronic administration of Madopar induced changes in the TSH and PRL responses which may be related to a state of relative deficiency of TIDA function, whereas with Sinemet hypothalamic DA function seemed to be preserved. On recalling that either treatment is equally effective in relieving the clinical features of Parkinsonism (Rinne & Mölsä 1979), our results would indicate that the state of TIDA function does not influence the competence of levodopa-DDI therapy to re-establish DA function in extrapyramidal centers.

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