Testicular response to human chorionic gonadotrophin in chronic hyperprolactinaemia

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Abstract. In order to evaluate the effect of hyperprolactinaemia on gonadal function in men, testicular stimulation by human chorionic gonadotrophin (hCG) (5000 IU/day, 3 consecutive days) was performed on 6 men with chronic hyperprolactinaemia and 6 control subjects. The following parameters were measured before and during the 4 consecutive days following the injections of hCG: the concentration in plasma of testosterone (T), oestradiol-17β (E₂), dihydrotestosterone (DHT) and the urinary excretion of testosterone glucuronide (TG) and 5α-androstane-3α,17β-diol glucuronide (3α-Diol G). The rises in T, E₂, DHT and the ratios of T/DHT and TG/3α-Diol G were similar in both groups, but the rises in TG and 3α-Diol G were lower in the hyperprolactaemic group after hCG. There was no correlation between the response of T and the increment of E₂ in either group. It is suggested that in men with chronic hyperprolactinaemia: 1) there is diminished testicular response to hCG; this could be due to chronic gonadotrophin deficiency or to a direct effect of hyperprolactinaemia on the testes, 2) there is no modulation of T synthesis through inhibition of aromatase activity and E₂ secretion and 3) the 5α-reduction of T is not deficient.

Studies of the testicular response to human chorionic gonadotrophin (hCG) in hyperprolactinaemia have yielded conflicting results. After hCG stimulation in men with drug-induced hyperprolactinaemia, Ambrosi et al. (1976) reported an increased response of plasma testosterone (T), Martikainen & Vihko (1982) noted a blunted response of plasma oestradiol-17β (E₂) suggesting an inhibitory influence of hyperprolactinaemia on aromatase activity, and Magrini et al. (1976) found no further change in T but a lower response of plasma dihydrotestosterone (DHT) indicating an inhibitory effect of hyperprolactinaemia on 5α-reductase activity.

The purpose of this study was to investigate the testicular response of T, E₂ and DHT, and to evaluate urinary excretion of testosterone glucuronide (TG) and 5α-androstane-3α,17β-diol glucuronide (3α-Diol G), an end-product of androgen metabolism, after hCG stimulation, in chronic hyperprolactinaemia.

Materials and Methods

Patients
Two groups of subjects were studied. Group 1 included 6 men, aged 25–44 years (mean = 33 years), who had prolactin-producing pituitary adenomata resulting in hyperprolactinaemia (Table 1). Group 2 included 6 male volunteers, aged 19–56 years (mean = 38 years), with no endocrine abnormalities.

Methods
Plasma was collected at 8.00 a.m. in order to measure prolactin (Prl) in both groups. The response of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) to luteinizing hormone-releasing hormone (LRH) was studied in groups 1 and 2, and plasma samples were obtained before and 15, 30, 60, 90 and 120 min after a...

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50 μg iv bolus injection of LRH at 8.00 a.m. The response to hCG was assessed in both groups by measuring the plasma concentration of T, E₂, DHT, and the urinary excretion of TG and 3α-Diol G, before (day 1) and for 4 consecutive days (days 2, 3, 4 and 5) after three im 5000 IU injections of hCG (days 1, 2 and 3). Blood samples were taken at 8.00 a.m. after an overnight rest and fast, and 24 h urine collections were started at 8.00 a.m.; hCG was injected at 9.00 a.m.

Immunoreactive Prl was measured by a double antibody homologous radioimmunoassay (RIA) (standard Prl: 42 IU WHO 71/222). Inter- and intra-assay coefficients of variation were 9 and 7%, respectively. LH and FSH were determined by RIA (LH 68/40 MRC, FSH 68/39 MRC). Inter- and intra-assay coefficients of variation were 18 and 5%, respectively. T and DHT were measured by RIA (Kuttenn et al. 1977). E₂ was determined by RIA (Castanier & Scholler 1970). TG and 3α-Diol G were determined by RIA (Wright et al. 1978).

Statistical analysis was performed using non-parametric tests: the significance of increment in each group was assessed by the Wilcoxon test, the comparisons of basal values and increment values of patient and control groups were by the Mann-Whitney U-test, and the correlation between the increment of T and E₂ in each group by the Spearman’s rank-test. A P-value greater than 0.05 was not considered significant. All reported values represent the mean ± se.

Results

The mean Prl level was 6932 ± 8421 ng/ml in group 1, and 7 ± 5 ng/ml in group 2 (P < 0.005). Mean basal LH and FSH were similar in groups 1 and 2, and increased significantly after LRH injection. The response of LH was lower in group 1
Correlation between the increments of T and E₂ following hCG in hyperprolactinaemic (group 1) and normoprolactinaemic (group 2) subjects.

<table>
<thead>
<tr>
<th>T increment (ng/ml)</th>
<th>E₂ increment (pg/ml)</th>
<th>Correlation coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n = 6)</td>
<td>4.79 ± 2.12</td>
<td>58 ± 48</td>
</tr>
<tr>
<td>Group 2 (n = 6)</td>
<td>7.28 ± 1.73</td>
<td>89 ± 42</td>
</tr>
</tbody>
</table>
reported a stimulatory action of PRL on LH binding by Leydig cells. Rubin et al. (1978) reported a T increase after haloperidol-induced acute hyperprolactinaemia, Nakagawa et al. (1982) found a T decrease during metoclopramide-induced hyperprolactinaemia over a period of 6 days, while Falaschi et al. (1978) did not observe any change in T concentrations during metoclopramide-induced hyperprolactinaemia over a period of 6 weeks. Ambrosi et al. (1976) reported an augmenting effect of sulpiride-induced hyperprolactinaemia on plasma T to 5000 IU hCG in normal men. Martikainen & Vihko (1982) found a decreased E2 response to hCG during sulpiride-induced hyperprolactinaemia which resulted in a higher although non-significant T secretion. In fact E2 is able to inhibit T synthesis at the testicular level by acting on 17α-hydroxylase and 17-20 desmolase (Samuels et al. 1964). An inhibitory action of PRL on E2 synthesis due to aromatase inhibition has also been reported by Dorrington & Gore-Langton (1981) in granulosa cell culture. Magrini et al. (1976) found that sulpiride produced no further increase in plasma T following 2000 IU hCG, but that there was a defect in the conversion of T to DHT, indicating an inhibition of 5α-reductase activity by hyperprolactinaemia.

In chronic hyperprolactinaemia due to PRL adenoma, T is usually low (Carter et al. 1978; Franks et al. 1978); this is not only the result of the destruction of LH and FSH cells by the large size of the tumour usually found in these patients, since T increases after PRL normalization by bromocriptine. Altered negative feedback control of gonadotrophin secretion and diminished LRH secretion due to hyperprolactinaemia would explain the fact that low plasma T levels are not accompanied by elevated gonadotrophin concentrations (Carter et al. 1978; Franks et al. 1978). The response of LH and FSH to LRH is within the normal range and the rise in plasma T concentrations following hCG administration is significant (Carter et al. 1978; Franks et al. 1978). In this study, the rise in urinary TG concentrations following hCG is significantly lower in the hyperprolactinaemic group, but it should be remembered that in chronic gonadotrophin deficiency, the testicular response to hCG may be poor; therefore a lower testicular response to hCG in group 1 does not necessarily mean gonadal resistance to LH induced by hyperprolactinaemia. The rise in plasma E2 concentrations following hCG is similar in both groups and was not correlated with T response. The rise in urinary 3α-DiolG concentrations under hCG is significantly lower in the hyperprolactinaemic group, but T/DHT and TG/3α-DiolG ratios are similar in both groups. If a relative gonadal resistance to LH and a partial deficiency in 5α-reduction exist in hyperprolactinaemic men, these could be overcome by supraphysiological stimulation of the testes with 5000 IU of hCG on 3 consecutive days.

In conclusion, the present study demonstrates that in men with chronic hyperprolactinaemia due to PRL adenoma:

There is a relatively low androgen response to hCG. This is probably due to the longstanding gonadotrophin deficiency. However, an element of testicular resistance due to hyperprolactinaemia cannot be excluded,

there is a normal oestrogen response to hCG, not correlated with androgen response. Thus, PRL does not seem to modulate androgen synthesis through inhibition of aromatase activity and the 5α-reduced metabolites of androgens parallel androgen production following hCG. This argues against an inhibitory action of hyperprolactinaemia on 5α-reductase activity.

However, studies on a larger group of patients with re-evaluation of gonadal responses to hCG after normalization of PRL by medical treatment would be necessary before a definite conclusion could be reached.

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References


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