Indirect evidence of chronic Leydig cell desensitization in Klinefelter’s syndrome

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Abstract. The basal plasma 17α-hydroxyprogesterone (17-OHP) and testosterone (T) levels were proportionally decreased in 10 hypergonadotropic patients with Klinefelter’s syndrome. The ratio 17-OHP to T was however about twice as high as in 10 eugonadal male controls, suggesting the presence of a block in the conversion of 17-hydroxylated steroids to androgens in the Klinefelter patients under basal circumstances. Administration of human chorionic gonadotrophin (hCG, 1500 IU im daily for 3 days) to the Klinefelter patients disclosed a response pattern quite different from that observed in controls. In the control subjects 17-OHP and the ratio 17-OHP/T sharply rose to maximum values at 24 h after the first injection. Thereafter both progressively fell to lowest values at 72 h, when T levels reached their maximum. In the Klinefelter patients the T response to hCG administration was greatly diminished but the 17-OHP response was similar to that in the controls. Maximum 17-OHP and 17-OHP/T values however were not achieved until 72 h after the first injection when T levels also reached their maximum. Unlike in the controls in the Klinefelter patients maximum 17-OHP and T increments and the 17-OHP and T levels 48 and 72 h after the injection were positively correlated.

Together the findings of a decreased T synthesis and reserve in the presence of relative 17-OHP accumulation, further increasing after acute hCG administration in a pattern quite different from that in normal men, suggest that in Klinefelter’s syndrome the Leydig cells may be chronically desensitized by the persistent endogenous hypergonadotropism.

Recently accumulation of 17α-hydroxyprogesterone (17-OHP) relative to testosterone (T) has been demonstrated in patients with Klinefelter’s syndrome (not in normal men), studied 72 h after the first of three daily injections of human chorionic gonadotrophin (hCG), suggesting that the later steps in steroid biosynthesis may be rate limiting in this syndrome (Smals et al. 1978). Very recently however, in normal men also a transient accumulation of 17-OHP relative to T has been found, reaching its maximum 24 h after a single or first of 2 or 3 daily injections and the nadir at 72 h (Forest et al. 1979; Smals et al. 1979, 1980a,b; Glass 1979). These data have been interpreted as indirect evidence of acute hCG induced Leydig cell desensitization in man (Forest et al. 1979; Glass 1979), analogous to that previously demonstrated in rats (Cigorraga et al. 1979; Haour & Saez 1978; Saez et al. 1979; Dufau et al. 1979a,b). In Klinefelter’s syndrome endogenous gonadotrophins are chronically elevated and therefore a different response pattern of 17-OHP and T to short term exogenous gonadotrophin administration would be expected between 0 and 72 h as in normal men. The present study reports on the profiles of both steroids in the basal state and 24, 48 and 72 h after the first of 3 daily injections of hCG in normal men and patients with Klinefelter’s syndrome.

Materials and Methods

Ten hypergonadotropic patients with Klinefelter’s syndrome (karyotype, 47 XXY; age 31.3 ± 8.8 years) and 10 eugonadotropic male controls (age 31.0 ± 12.7 years) were given 1500 IU of hCG (Pregnyl®, Organon) daily...
for 3 days and blood for 17-OHP and T determination was sampled at 8 a.m. before and at 24, 48 and 72 h after the first injection. Informed consent was obtained from all subjects.

Plasma 17-OHP and T levels were measured by radioimmunoassay after a paper chromatographic purification step (intra-assay coefficients of variation, respectively 6.1 and 4%, Smals et al. 1976, 1978). To avoid inter-assay variation all samples from one subject were measured in the same series.

Statistical analysis was performed using Wilcoxon’s signed rank test, Wilcoxon’s two sample test, Spearman’s rank correlation test and Fisher χ² test. The means ± 1 SD are given.

Results

Basal 17-OHP and T levels and the 17-OHP to T ratio (Fig. 1, Table 1)

The mean basal 17-OHP and T levels in the

Fig. 1.
Effect of hCG administration (1500 IU im daily for 3 days) on the individual (—) and mean (——) plasma testosterone (T) and 17-hydroxyprogesterone (17-OHP) levels and the ratio 17-OHP/T at 24, 48 and 72 h after the first injection in 10 normal men and 10 patients with Klinefelter’s syndrome.
**Table 1.**

Mean absolute and relative plasma testosterone (T) and 17-hydroxyprogesterone (17-OHP) levels and 17-OHP/T ratios before (day 0) and after 1, 2 and 3 days of hCG administration (Pregnyl®. Organon 1500 IU) in 10 normal men and 10 patients with Klinefelter’s syndrome.

<table>
<thead>
<tr>
<th>Day</th>
<th>Plasma testosterone</th>
<th>Plasma 17-OHP</th>
<th>17-OHP/T</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ng/100 ml</td>
<td>% of day 0</td>
<td>ng/100 ml</td>
</tr>
<tr>
<td>Control subjects (n = 10), mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>673 ± 234</td>
<td>100</td>
<td>188 ± 71</td>
</tr>
<tr>
<td>1</td>
<td>860 ± 209</td>
<td>131 ± 32</td>
<td>415 ± 168</td>
</tr>
<tr>
<td>2</td>
<td>1262 ± 262</td>
<td>198 ± 50</td>
<td>384 ± 136</td>
</tr>
<tr>
<td>3</td>
<td>1376 ± 311</td>
<td>217 ± 67</td>
<td>317 ± 109</td>
</tr>
<tr>
<td>Klinefelter patients (n = 10), mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>191 ± 87</td>
<td>100</td>
<td>92 ± 62</td>
</tr>
<tr>
<td>1</td>
<td>245 ± 103</td>
<td>137 ± 40</td>
<td>155 ± 86</td>
</tr>
<tr>
<td>2</td>
<td>307 ± 170</td>
<td>162 ± 38</td>
<td>219 ± 122</td>
</tr>
<tr>
<td>3</td>
<td>349 ± 190</td>
<td>189 ± 53</td>
<td>226 ± 102</td>
</tr>
</tbody>
</table>

Klinefelter patients were significantly lower than in the controls (P < 0.01 and < 0.001, respectively). In the Klinefelter patients a positive correlation was found between the basal 17-OHP and T levels (r = +0.76, P < 0.02), not however in the control subjects (r = +0.02, P > 0.10). The mean basal 17-OHP/T ratio in the Klinefelter patients was about twice as high as in the normal men (P < 0.025).

**Effect of hCG administration on 17-OHP and T levels and the 17-OHP to T ratio (Fig. 1, Table 1)**

hCG administration gradually increased the mean T levels in the control subjects to maximum 2.2 times the baseline value at 72 h after the first injection and in the Klinefelter patients to 1.9 × baseline (P > 0.10 vs. controls). At all time intervals however the absolute T increments in the Klinefelter patients were significantly lower (3 to 5 times) than in the controls (P < 0.02 < < 0.001). Maximum T levels were achieved after 72 h in 9 out of 10 control subjects and in 7 out of 10 Klinefelter patients (P > 0.10).

After hCG administration the mean plasma 17-OHP levels in the control subjects increased to maximum values 2.3 × baseline at 24 h (P < 0.01 vs. 0 h) and thereafter significantly fell to values 2.1 and 1.7 × baseline at 48 and 72 h, respectively (P < 0.05 vs. 24 and 48 h). In the Klinefelter patients plasma 17-OHP levels gradually increased to 1.7 × baseline at 24 h, P < 0.01 vs. 0 h) 2.4 × at 48 h (P < 0.01 vs. 24 h) and 2.8 × at 72 h (P < 0.05 vs. 24 h, P > 0.1 vs. 48 h). The mean relative increase at 72 h in the Klinefelter patients was significantly higher than in the control subjects (P < 0.01). The mean absolute 17-OHP increment in the Klinefelter patients was about 4 times lower than in the controls at 24 h (P < 0.01), but almost equal at 72 h (P < 0.10). The maximum absolute 17-OHP increments in both groups did not differ significantly (0.05 < P < 0.10). In 7 out of 10 control subjects, but none of the Klinefelter patients, maximum 17-OHP levels were achieved after 24 h (P < 0.01). Reversely, in 7 out of Klinefelter patients but only one of the controls maximum levels were reached after 72 h (P < 0.025). In the Klinefelter patients, but not in the control subjects, a significant positive correlation was found between the maximum 17-OHP and T increments (r = +0.82, P < 0.01), the maximum 17-OHP and T values (r = +0.83, P < 0.01) and the 17-OHP and T values achieved after 48 and 72 h (r = +0.67 and +0.87, P < 0.05 and < 0.01, respectively).

In each of the control subjects the 17-OHP/T ratio increased and reached its maximum, (1.7 × baseline) (P < 0.01) 24 h after the first injection. Thereafter the 17-OHP/T ratio fell to 1.1 × baseline at 48 h (P < 0.01 vs. 24 h) and 0.8 × baseline at 72 h (P < 0.01 and < 0.02, respectively vs. 24 and 48 h and < 0.05 vs. baseline). In the Klinefelter
patients the already elevated 17-OHP/T ratio further increased to 1.3 × baseline\( (P < 0.05\) vs. basal level) at 24 h, 1.5 × baseline, \( (P < 0.01\) vs. 0 h and <0.05 vs. 24 h) at 48 h and 1.6 × baseline at 72 h, \( (P < 0.01\) vs. basal level, \( P > 0.1\) vs. 24 and 48 h). In 7 out of 10 Klinefelter patients max. 17-OHP/T ratios were reached only after 48 or 72 h, whereas in all control subjects maximum 17-OHP/T ratios were achieved after 24 h. At 24 h after the first injection the 17-OHP/T ratio in the Klinefelter patients was no longer different from that in the control subjects, but after 48 and 72 h the mean value in the patients was twice or even thrice the ratio in the controls \( (P < 0.001)\).

Discussion

In the group of Klinefelter patients from the present study the mean basal T level was lower than in an earlier study of this laboratory, whereas the mean basal 17-OHP levels, although distinctly decreased, were about equal in both groups (Smals et al. 1978). The resulting mean basal 17-OHP/T ratio in the patients from the present study therefore was significantly higher than in the control subjects. However in both the present and our earlier study the 17-OHP/T ratio in the individual Klinefelter patients ranged from normal to higher than normal levels, whereas 17-OHP and T levels were proportionally decreased.

A similar accumulation of 17-OHP relative to T earlier was demonstrated by Stewart-Bentley & Horton (1973). However the 17-OHP levels in the patients with Klinefelter's syndrome in their study were normal or even elevated in contrast to data in our studies and in a study by other investigators (Ruder et al. 1974).

The data in the present and our earlier study at least suggest that under basal circumstances testicular steroidogenesis in Klinefelter's syndrome is globally attenuated, due to a defect early in the steroidogenic pathway affecting both 17-OHP and T synthesis. In addition to this early lesion, the accumulation of 17-OHP relative to T and the tight correlation between the levels of these hormones in the Klinefelter patients unlike in the control subjects, point to another defect situated at a locus between 17-OHP and T. It is tempting to speculate that in Klinefelter's syndrome the persisting sustained endogenous hypergonadotropism induces a state of chronic desensitization of testicular steroidogenesis analogous to that reported after single or repeated gonadotrophin administration in rats, with down-regulation of the LH receptor, inhibition of testicular steroidogenesis – due to a blockade at the level of 17 hydroxylase and even more 17,20 lyase- and a diminished response to subsequent gonadotrophin administration (Cigorraga et al. 1978; Haour & Saez 1978; Saez et al. 1979; Dufau et al. 1979a,b; Belanger et al. 1979).

If a similar chronic, gonadotrophin induced enzyme blockade were operative in Klinefelter's syndrome it could offer a plausible explanation for both the proportionally decreased 17-OHP and T synthesis and the elevated 17-OHP or T ratio. Such mechanism of chronic desensitization also might account for the altered response pattern of both 17-OHP and T to short term exogenous hCG administration in this syndrome. It is well known that in patients with Klinefelter's syndrome hCG stimulation evokes a much lower T increase than in control subjects (Ruder et al. 1974; Paulsen et al. 1968; Smals et al. 1974). Previous chronic gonadotrophin stimulation may account for this blunted response. In rats (Cigorrage et al. 1978; Saez et al. 1979; Dufau et al. 1979a,b) and very recently also in eugonadal man (Smals et al. 1979; Saez & Forest 1979) evidence has been adduced for testicular refractoriness to subsequent hCG stimulation after previous gonadotrophin administration due to acute Leydig cell desensitization.

In the present and previous studies hCG administration to male controls was accompanied by a temporary increase of 17-OHP and the 17-OHP to T ratio, reaching its maximum 24 h after a single or first of 3 daily injections (Forest et al. 1979; Smals et al. 1979, 1980a,b). Thereafter both parameters decreased to a nadir at 72 h, the 17-OHP/T ratio even falling below baseline values. Partial hCG induced (oestrogen mediated) inhibition of 17,20 lyase has been thought to be responsible for this temporary 17-OHP accumulation (Haour & Saez 1978; Saez et al. 1979; Dufau et al. 1979a,b). In the Klinefelter patients however a quite different response pattern of 17-OHP and the ratio 17-OHP/T was observed. Whereas 17-OHP and the ratio 17-OHP/T increased within 24 h in most patients, maximum values were not obtained until 72 or 48 h in most of them. Only in one patient with the highest basal T level, a normal 17-OHP/T response to hCG administration was observed with a 24 h maximum and a 72 h 17-OHP/T ratio below the baseline value. Furthermore as in the basal state a
close relationship was found between the maximum absolute 17-OHP and T increments and the 17-OHP and T levels achieved at 48 and 72 h after the injection. These data suggest that in Klinefelter's syndrome acute exogenous gonadotrophin administration by further increasing oestrogen synthesis may intensify the suppression of enzyme activities, at the 17,20-lyase step even more than at the 17-hydroxylase locus. The increased output of 17-OHP however partially might compensate for the enzymatic block and thus a new equilibrium is established between 17-OHP and T, at a relatively higher 17-OHP level. Together these data suggest that in Klinefelter's syndrome endogenous hypergonadotropism might be the main cause of the defective steroidogenesis by a complex process of chronic Leydig cell desensitization and down-regulation of testicular steroid biosynthesis.

References


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