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Naltrexone Does Not Affect Adrenal Steroidogenesis in Women with Hirsutism/Oligomenorrhea

Jeffrey A. Jackson, MD,* Thomas J. Wincek, MD, PhD,† and Jose F. Pliego, MD‡

We studied the effects of the oral opiate receptor antagonist naltrexone on basal and ACTH-stimulated adrenal steroid levels in six women with hirsutism/oligomenorrhea and preexisting elevation of serum dehydroepiandrosterone sulfate. One of the six patients met the criteria for partial 3β-hydroxysteroid dehydrogenase deficiency. No statistical differences were detected in steroid levels or ratios before and after 14 days of 50 mg/day of naltrexone. Thus, we find no support for the hypothesis that opioid peptides acting through opiate receptors (predominantly μ subtype) modulate the abnormal adrenal androgen secretion seen in these women with hirsutism/oligomenorrhea. (Henry Ford Hosp Med J 1987;35:194-7)

Considerable clinical and experimental evidence has suggested that a non-ACTH pituitary factor may control adrenal androgen secretion (1-4). β-Endorphin, a proopiomelanocortin-derived opioid peptide, has been considered as a possible modulator of adrenal androgen synthesis (1). Abnormal adrenal androgen levels occur frequently in patients with polycystic ovary syndrome (5-8), and elevated β-endorphin levels have also been reported in this syndrome (9,10). Consequently, we studied the effects of an oral opiate receptor antagonist, naltrexone, on basal and ACTH-stimulated adrenal steroid levels in a group of women with hirsutism/oligomenorrhea and preexisting elevation of serum dehydroepiandrosterone sulfate (DHEA-S).

Materials and Methods

Six patients, aged 22 to 34, with at least three months of untreated hirsutism [mean Ferriman-Gallwey (11) index 10], prior oligomenorrhea by history, and previously determined elevations of serum DHEA-S (mean 4,646 ± 1,300 ng/mL; normal 820 to 3,380 ng/mL) participated in the study after giving informed consent (Table 1). All patients had previously demonstrated suppressibility of serum DHEA-S by dexamethasone or prednisone and/or normal adrenal computed tomography to exclude androgen-producing adrenal neoplasms. None had a history of liver disease or narcotic abuse. Testing was performed in the early follicular phase for the patients who had a regular cycle at the time of the study (patients 1 and 6); the other four subjects were initiated randomly. Effective barrier contraception was recommended throughout the study period.

Prenaltrexone and postnaltrexone blood sampling was performed by indwelling catheter between 8 AM and 9 AM and one hour after intravenous administration of 0.25 mg of synthetic 1-24-ACTH (Cortrosyn™, Organon, West Orange, NJ). Naltrexone (Trezan™, Du Pont, Wilmington, DE), 50 mg orally, was given daily for 14 days (28 days for patient 2 only), with the final dose at 6 AM on the final day of ACTH testing.

Serum gonadotropins (Leeco Diagnostics, Southfield, MI), prolactin (Serono Diagnostics, Inc, Randolph, MA), estradiol (Radioassay Systems, Carson, CA), testosterone and DHEA-S (Diagnostic Products Corp, Los Angeles, CA), and plasma ACTH (edetic acid sample separated and stored at −20°C prior to assay—Radioassay Systems) were measured by specific radioimmunoassays prior to ACTH stimulation. Serum DHEA, 17-hydroxyprogrenolone, 17-hydroxyprogesterone, androstenedione (Endocrine Sciences, Tarzana, CA), and cortisol (Diagnostic Products Corp) were measured by specific radioimmunoassays both before and after ACTH stimulation. Serum transaminases were measured by automated analyzer.

Mean hormonal values prenaltrexone and postnaltrexone were compared statistically by using paired t tests. The confidence intervals for correlations among various hormonal levels and ratios were examined for indications of relationships. P-values greater than 0.05 (one-tailed) were considered not statistically significant. Mean values are expressed as mean ± SD.

Results

Baseline hormonal concentrations in the six subjects are shown in Table 1. Prenaltrexone means (Table 2) for serum DHEA-S and testosterone were above the reference range. All patients were normoprolactinemic; four had ratios of luteinizing hormone to follicle-stimulating hormone two subjects respectively.

Initial ACTH stimulation partially decreased DHEA-S and testosterone, and DHEA-S and testosterone were decreased after ACTH stimulation. Naltrexone did not attenuate the ACTH stimulation.


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to follicle-stimulating hormone greater than 2.0. Coincidental ovulation occurred just prior to and on day 1 of testing in two subjects who had oligomenorrhea (patients 3 and 2, respectively).

Initial ACTH stimulation failed to uncover any patients with partial defects in 21-hydroxylase activity (stimulated 17-hydroxypregnenolone and DHEA levels, and 17-hydroxypregnenolone to 17-hydroxyprogesterone levels. Table 2). Patient 4 met all previously proposed criteria for suspected 3β-hydroxysteroid dehydrogenase deficiency (Figure; stimulated 17-hydroxypregnenolone and DHEA levels, and DHEA to 17-hydroxyprogesterone, 17-hydroxypregnenolone to cortisol, and DHEA to androstenedione ratios > 2 SD above those of normal controls) (12). All patients had normal cortisol responses to ACTH.

Postnaltrexone means for ACTH, prolactin, gonadotropins, and all of the steroid levels and ratios measured (Table 2) did not differ significantly from pretreatment values. Correlation matrix examination showed no statistically significant relationships between estradiol and Δ3-steroid levels or Δ4-steroid Δ4-steroid ratios.

Naltrexone treatment caused no alterations in liver transaminase levels. Four subjects experienced mild nausea without vomiting in the first three to seven days of therapy; pretreatment and postnaltrexone body weights did not differ statistically.

### Table 1
Clinical Data and Baseline Hormonal Levels

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (year)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Hirsutism Index*</th>
<th>Menses</th>
<th>ACTH (pg/mL)</th>
<th>PRL (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>158</td>
<td>55.7</td>
<td>7</td>
<td>Regular</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>158</td>
<td>57.3</td>
<td>7</td>
<td>Regular</td>
<td>30</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>173</td>
<td>86.4</td>
<td>11</td>
<td>Irregular</td>
<td>58</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>163</td>
<td>100.5</td>
<td>14</td>
<td>Irregular</td>
<td>51</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>158</td>
<td>55.7</td>
<td>9</td>
<td>Regular</td>
<td>37</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
<td>170</td>
<td>83.2</td>
<td>28</td>
<td>Irregular</td>
<td>37</td>
<td>15</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>43 ± 12</td>
<td>13 ± 2</td>
</tr>
</tbody>
</table>

Reference range: < 100 < 16

### Table 2
Baseline and ACTH-Stimulated Steroid Levels Before and After Naltrexone

<table>
<thead>
<tr>
<th>Steroid*</th>
<th>Before Naltrexone†</th>
<th>After Naltrexone‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA-S (ng/mL)</td>
<td>3,856 ± 808 (3,016-5,180)</td>
<td>3,856 ± 1,385 (2,290-6,396) NS</td>
</tr>
<tr>
<td>Testosterone (ng/mL)</td>
<td>1.0 ± 0.2 (0.8-1.2)</td>
<td>0.9 ± 0.2 (0.6-1.1) NS</td>
</tr>
<tr>
<td>17-Preg (ng/mL)</td>
<td>2.3 ± 1.5 (0.6-4.3)</td>
<td>1.9 ± 1.4 (0.5-4.3) NS</td>
</tr>
<tr>
<td>17-Preg (ng/mL)</td>
<td>1.0 ± 0.7 (0.2-1.9)</td>
<td>0.8 ± 0.8 (0.4-2.4) NS</td>
</tr>
<tr>
<td>DHEA (ng/mL)</td>
<td>6.3 ± 2.9 (2.4-10.8)</td>
<td>6.9 ± 2.7 (4.8-9.9) NS</td>
</tr>
<tr>
<td>Androstenedione (ng/mL)</td>
<td>2.7 ± 1.3 (1.5-5.0)</td>
<td>2.8 ± 1.5 (1.8-5.7) NS</td>
</tr>
<tr>
<td>Stimulated 17-Preg (ng/mL)</td>
<td>12.2 ± 6.1 (5.9-20.6)</td>
<td>11.0 ± 3.9 (7.7-17.6) NS</td>
</tr>
<tr>
<td>Stimulated cortisol (μg/dL)</td>
<td>37.3 ± 8.3 (27.1-48.9)</td>
<td>36.1 ± 4.9 (30.4-42.1) NS</td>
</tr>
</tbody>
</table>

*Stimulated = steroid level one hour after ACTH administration.
†Values are expressed as the mean ± SD; the range is in parentheses.
‡Note: DHEA-S = dehydroepiandrosterone sulfate, 17-Preg = 17-hydroxypregnenolone, and 17-Preg = 17-hydroxyprogesterone.
Discussion

Several lines of evidence have suggested a possible role of opioid peptides in modulating adrenal androgen synthesis and secretion. β-endorphin levels strongly correlate with serum DHEA-S in children undergoing normal adrenarche (13) and decline in mid-life coincident with adrenopause (14). Opiate receptors have been demonstrated in the adrenal cortex (15) with partial 3β-hydroxysteroid dehydrogenase deficiency. (17). Ports of elevated plasma P-endorphin in polycystic ovary syndrome. These observations, along with reported in normal women (12). Values for patient 4 who had partial 3β-hydroxysteroid dehydrogenase deficiency. (17-Preg = 17-hydroxypregnenolone, 17-Prog = 17-hydroxyprogesterone, Adione = androstenedione, and DHEA = dehydroepiandrosterone.)

lack of elevation of serum DHEA-S in obese, normally menstruating women (20).

Dynamic ACTH testing has uncovered subtle adrenal enzyme deficiencies, particularly 21-hydroxylase (12,21) and 3β-hydroxysteroid dehydrogenase (12,22), in a variable percentage of women with hirsutism/oligomenorrhea, many of whom have baseline adrenal androgen elevations. One of our patients had partial 3β-hydroxysteroid dehydrogenase deficiency by previously described criteria. Lucky et al (23) proposed that the women in their study who had acne and manifested ACTH hyperresponsiveness of 17-hydroxypregnenolone, DHEA, and/or androstenedione with normal cortisol responses might have an acquired condition, "exaggerated adrenarche," related to relative hyperplasia of the zona reticularis rather than a congenital enzyme defect. We have not studied family members of our patient with the partial 3β-hydroxysteroid dehydrogenase defect, but she did not give a history of premenarchal hirsutism or early pubarche, in contrast to some patients described by Pang et al (12).

Several investigators have proposed that the adrenal abnormalities in polycystic ovarian syndrome may be mediated by a pituitary-derived adrenal androgen-stimulating factor (6,7,16). This would not be surprising given the other hypothalamic-pituitary aberrations which are commonly encountered in polycystic ovary syndrome (24,25). Such a pituitary factor might affect ACTH responsiveness by modulating adrenal enzyme activities, particularly 3β-hydroxysteroid dehydrogenase (26). Our study indicates that opioid peptides acting through opiate receptors (predominantly μ subtype) are not responsible for the adrenocortical steroidogenic abnormalities observed in these women with hirsutism/oligomenorrhea.

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