Naloxone administration does not affect gonadotrophin secretion in male patients with isolated hypogonadotrophic hypogonadism

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Abstract. We evaluated the gonadotrophin response to acute naloxone administration (10 mg iv) in 4 male patients with isolated hypogonadotrophic hypogonadism (age range 18.5–26 years) before and after pituitary priming with daily infusions of GnRH (25 µg/h for 4 h) for 4 days.

A blunted gonadotrophin response to acute GnRH administration (100 µg iv) and a lack of response to naloxone was observed before pituitary priming. After repeated infusions of GnRH, pituitary gonadotrophin responsiveness to GnRH was restored, whilst naloxone still did not affect gonadotrophin levels. Our data suggest that in male isolated hypogonadotrophic hypogonadism (1) the lack of pituitary response to naloxone is not due to pituitary hyporesponsiveness to GnRH; (2) endogenous opioids do not exert any inhibitory influence on GnRH secreting neurons and thus are not involved in the pathogenesis of this disease.

Endogenous opioids appear to be important regulators of gonadotrophin secretion through modulation of the pulsatile release of GnRH (Grossman et al. 1981; Moult et al. 1981). Naloxone, a potent and selective opioid antagonist, increased gonadotrophin levels in normal men (Delitala et al. 1981), in normal cycling women during the late follicular and mid-luteal phase (Quigley & Yen 1980), while no effect was found in children at the onset of puberty (Fraioli et al. 1984) or in post-menopausal women (Reid et al. 1983).

A significant role for endogenous opioids in gonadotrophin release has also been suggested in hypothalamic amenorrhoea (Quigley et al. 1980b) and hyperprolactinaemia (Quigley et al. 1980a; Grossman et al. 1982) but not in patients with weight-loss amenorrhoea (Grossman et al. 1982).

The hypothesis that a suppressive effect of endogenous opioid peptides could be involved in the pathogenesis of male hypogonadotrophic hypogonadism has been recently tested in patients affected by Kallmann’s syndrome by the administration of naloxone (Veldhuis et al. 1982); in this study naloxone showed no significant effect on gonadotrophin secretion.

Since the lack of response to naloxone might be due to pituitary hyporesponsiveness to GnRH, we evaluated the gonadotrophin response to acute naloxone administration in 4 males affected by isolated hypogonadotrophic hypogonadism before and after pituitary priming with daily infusions of GnRH for 4 days.

Material and Methods

Control subjects

Seventeen healthy men (age range 22–51 years) were studied as controls. They provided informed consent before participation in the study. All tests were performed after an overnight fast and started at 08.00–09.00 h, 30 min after the insertion of a needle in an antecubital vein. The needle was kept patent with a slow infusion of physiological saline.

Protocol I. Eleven control subjects (age range 22–51 years) were selected to receive a standard dose of 100 µg of synthetic GnRH (Relisorm, Serono) iv as a bolus. Blood was sampled –15, 0, 15, 30, 60 and 120 min after GnRH administration.
Protocol II. Six normal men (age range 25–33 years) received on 2 different days, at least 5 days apart, in random order and in single blind fashion, a bolus of 1 ml of saline or of 1 ml of naloxone hydrochloride containing 10 mg/ml (Naloxone hydrochloride, Endo Laboratories Inc., New York). Blood was sampled −30, 0, 15, 30, 45, 60, 90 and 120 min after placebo or naloxone administration.

Hypogonadotropic patients

Four male patients affected by isolated hypogonadotrophic hypogonadism (age range 18.5–26 years) gave their written informed consent to the study. The main clinical and endocrine features of the patients are reported in Table 1.

Each patient underwent the following protocol:

Day 1. Naloxone administration was performed as in control subjects (protocol II).

Day 2. GnRH administration was performed as in control subjects (protocol I).

Day 3–6. Twenty-five μg/h of synthetic GnRH in 250 ml of saline was infused during 4 h starting between 08.00–09.00 h.

Day 7. As in day 1.

Day 8. As in day 2.

Methods

Blood samples were stored at 4°C and centrifuged within 1 h; plasma samples were stored at −20°C until assayed.

Plasma LH and FSH was measured by double antibody RIA's with 125I labelled antigens and antisera provided by Biodata (Milan, Italy). Gonadotrophin concentrations are expressed in mIU/ml (reference standard: 26 IRP-HMG).

Samples from each subject were assayed in duplicate in a single assay. The sensitivity of the method was 1 mU/ml for FSH and 0.7 mU/ml for LH. The within-assay coefficients of variation were 5.7% for FSH and 7.5% for LH; the between-assay coefficients of variation were 6.5% for FSH and 8.7% for LH.

Plasma testosterone was measured by RIA after paper chromatography of plasma extracts (Forti et al. 1974).

Statistical analysis was performed with Student's t-test for paired data. Results are reported as the mean ± SEM.

Table 1.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Previous therapy</th>
<th>Testicular volume2 (ml)</th>
<th>Plasma T3 (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>DX</td>
<td>SX</td>
</tr>
<tr>
<td>I</td>
<td>21</td>
<td>none</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>21</td>
<td>none</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>III</td>
<td>18.5</td>
<td>none</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>IV</td>
<td>26</td>
<td>HCG + FSH1</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

1 Therapy was withdrawn 3 months before.
2 Measured with Prader orchidometer.
3 Normal range: 10.42–34.72 nmol/l.

Results

In 6 normal controls naloxone administration significantly increased LH levels (P < 0.05 vs baseline at 45 and 90 min), while no modifications were observed after iv placebo administration. The mean LH values found 15, 45 and 60 min after naloxone were significantly higher than after placebo (Table 2).

No significant modifications of FSH levels were observed either after naloxone or placebo administration (Table 2).

In the hypogonadotrophic patients naloxone administration did not affect LH (Fig. 1) and FSH levels either before or after prolonged exposure to GnRH. In the same patients in basal conditions GnRH elicited a subnormal gonadotrophin response which was restored after repeated infusion of GnRH (Figs. 2 and 3).

Table 2.

<table>
<thead>
<tr>
<th>Time</th>
<th>LH</th>
<th>FSH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Naloxone</td>
</tr>
<tr>
<td>−30</td>
<td>8.9 ± 0.6</td>
<td>9.3 ± 1.2</td>
</tr>
<tr>
<td>0</td>
<td>8.5 ± 0.8</td>
<td>9.2 ± 0.8</td>
</tr>
<tr>
<td>15</td>
<td>8.7 ± 0.8</td>
<td>12.4 ± 1.5</td>
</tr>
<tr>
<td>30</td>
<td>9.0 ± 0.1</td>
<td>12.0 ± 1.5</td>
</tr>
<tr>
<td>45</td>
<td>8.4 ± 0.8</td>
<td>11.3 ± 0.9</td>
</tr>
<tr>
<td>60</td>
<td>8.6 ± 0.9</td>
<td>11.1 ± 0.5</td>
</tr>
<tr>
<td>90</td>
<td>10.0 ± 0.1</td>
<td>11.9 ± 0.9</td>
</tr>
<tr>
<td>120</td>
<td>10.4 ± 0.7</td>
<td>10.6 ± 0.7</td>
</tr>
</tbody>
</table>

Significance: vs time 0: 1P < 0.05, vs placebo: 2P < 0.05.
Effects of naloxone administration on LH plasma levels (mean ± SEM) in 4 male patients affected by isolated hypogonadotrophic hypogonadism before (■—■) and after (○—○) repeated infusions of GnRH. The shaded area shows the range of the response in 6 normal controls.

Effects of GnRH administration on LH plasma levels (mean ± SEM) in 4 male patients affected by isolated hypogonadotrophic hypogonadism before (■—■) and after (○—○) repeated infusions of GnRH. The shaded area shows the range of the response in 11 normal controls.
Discussion

There is considerable evidence that opioid peptides affect gonadotrophin secretion in different pathophysiological states in the human adult female (Quigley et al. 1980a,b; Lightman et al. 1981; Grossman et al. 1982), whilst few data have been reported in hypogonadotrophic males. Veldhuis et al. (1982), testing the hypothesis that endogenous opioids might be involved in the pathogenesis of hypogonadotrophic hypogonadism, found no effect of naloxone infusion on gonadotrophin secretion in boys with constitutional delayed puberty, children with idiopathic hypopituitarism and 3 adult males with Kallmann's syndrome.

It is well known that basal secretion of FSH and LH and the pituitary response to GnRH are reduced in males affected by hypogonadotrophic hypogonadism (Mortimer et al. 1973). In these patients, however, pituitary responsiveness can be restored after repeated infusions of exogenous GnRH (Snyder et al. 1979).

In our patients this treatment restored, as expected, pituitary responsiveness to GnRH, but naloxone administration still did not affect gonadotrophin levels.

Therefore our data demonstrate that in hypogonadotrophic hypogonadism the lack of response to naloxone is not due to pituitary hyporesponsiveness and that an increased opioid inhibition of GnRH secreting neurons is not involved in the pathogenesis of this disease.

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References


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