Impaired LH-RH Release by Estrogen in Women with Sulpiride-Induced Hyperprolactinemia.

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Abstract

The effects of hyperprolactinemia on the release of immunoreactive luteinizing hormone-releasing hormone (LH-RH) and luteinizing hormone (LH) in response to iv injection of 20 mg conjugated estrogens (Premarin®) were studied. Five normal cycling women were injected with Premarin on the morning of the 7th day of the first cycle (control cycle), and then the plasma levels of LH-RH, LH, and prolactin (PRL) were determined every 8 to 16 hours for 72 h. Two months later, the same women received 200 mg of oral sulpiride daily for 8 days from the 3rd day of the cycle (sulpiride treated cycle), and then the same protocol as in the control cycle was applied.

Mean (±SE) plasma levels of PRL on day 7 in the sulpiride treated cycle were significantly higher than those in the control cycle (118±24 ng/ml vs. 14±4 ng/ml, p<0.001). After estrogen injection, the mean percent increases in immunoreactive LH-RH at 32 h (control: 71±38% vs. sulpiride: 6±36%) and 40 h (154±38% vs. -5±21%) and in LH at the 48 h (175±89% vs. 57±57%) and 56 h (99±32% vs. 7±21%) were significantly (p<0.01 or p<0.05) suppressed in the sulpiride cycle.

These data suggest that the impaired positive feedback effect of estrogen on LH-release in hyperprolactinemic anovulatory women may be caused, at least in part, by disturbed LH-RH release.

It is well documented that hyperprolactinemia results in anovulatory conditions and that hyperprolactinemic women do not show the luteinizing hormone (LH) release after estrogen injection that is observed in normal cycling women (Glass et al., 1975; Aono et al., 1976; L’Hermite et al., 1978). Normalization of plasma prolactin (PRL) following bromocriptine treatment (Aono et al., 1979) and removal of prolactinomas by transsphenoidal surgery (Koike et al., 1982) restores the LH surge after estrogen administration and the ovulatory cycle. These findings suggest that the impaired release of LH in response to estrogen may be one reason for anovulation in hyperprolactinemic women. It is not clear whether PRL inhibits the secretion of pituitary LH directly or through impaired hypothalamic LH-releasing hormone (LH-RH) secretion. We recently observed the induction of a plasma LH-RH peak after estrogen injection in normal

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cycling women (Miyake et al., 1983).

In the present study, we investigated the effects of sulpiride-induced hyperprolactinemia on the release of LH-RH in response to estrogen injection.

Materials and Methods

In the control cycle, five normal cycling women aged 21 to 23 were injected with 20 mg of conjugated estrogens, Premarin® (Ayerst Labs., Rouses Point, N.Y.), on the morning of the 7th day of the cycle. Blood samples were taken between 8 and 9 a.m. from the 3rd to 7th day of the cycle and 0, 8, 24, 32, 40, 48, 56 and 72 h after Premarin injection and were stored at −15°C until assayed. Two months later, the same normal women received 200 mg of oral sulpiride daily for 8 days from the 3rd day of the cycle, and the same protocol as the control cycle was applied (sulpiride treated cycle). Informed consent of the volunteers to participate in the study was obtained.

Plasma PRL levels in the morning samples taken from the 3rd to 10th day of the cycle were determined by RIA (Aono et al., 1976). Plasma levels of LH-RH and LH in samples taken from 0 to 72 h after Premarin injection were determined by specific RIAs (Aono et al., 1972; Miyake et al., 1980). Plasma levels of FSH and estradiol on the morning of the 7th day were also assayed by RIAs (Aono et al., 1972 and 1978). The sensitivities and intraassay coefficients of variation of the assays were 0.6 pg/tube and 13.8% for LH-RH, 0.1 mIU/tube of the 2nd IRP-HMG and 13.3% for LH, 0.2 mIU/tube and 9.0% for FSH, 2.0 ng/tube and 4.3% for PRL, and 10.0 pg/tube and 4.0% for estradiol respectively. Statistical analyses of data were performed by split-plot type analysis of variance or Student’s t-test.

Results

Daily changes in plasma PRL levels with or without sulpiride treatment are shown in Fig. 1. The mean plasma levels of PRL in the control cycle were in the normal range throughout the study period, whereas those in the sulpiride treated cycle gradually increased from 19.6 ng/ml to 118.0 ng/ml on the 7th day and 159.8 ng/ml on the 10th day of the cycle, and all these levels after the 4th day were significantly (p <0.001) higher than those in the control cycle. The effects of sulpiride-induced hyperprolactinemia on the basal levels of LH-RH, LH, FSH and estradiol on the 7th day of the cycle when estrogen was injected are shown in Table 1. The mean plasma estradiol level in the sulpiride treated cycle was significantly lower than that in the control cycle (68.6±9.6 pg/ml vs. 101.4±20.6 pg/ml, p <0.05), but the levels of LH-RH, LH and FSH were not significantly different between the two cycles.

The percent changes in LH-RH and LH from the preinjection level are shown in Fig. 2. The LH-RH level in the control
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Table 1. Mean (±SE) levels of plasma immunoreactive LH-RH, LH, FSH and estradiol just before iv injection of 20 mg of conjugated estrogens on the 7th day of the cycle in the control and sulpiride treated cycle. The asterisk indicates a significant difference from the value in the control cycle (*p<0.05 by Student's t-test).

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Control cycle</th>
<th>Sulpiride treated cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH-RH (pg/ml)</td>
<td>4.5±0.9</td>
<td>3.8±0.8</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>8.5±2.0</td>
<td>8.2±1.5</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>6.3±0.3</td>
<td>7.2±0.3</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>101.4±20.6</td>
<td>68.6±9.6*</td>
</tr>
</tbody>
</table>

Fig. 2. Mean percent changes in immunoreactive LH-RH and LH in plasma after iv injection of 20 mg of conjugated estrogen (Premarin*) in the control and sulpiride treated cycles. Vertical bars show standard errors of means. Asterisks indicate a significant difference from the control group (*p<0.05, **p<0.01 by analysis of variance).

We recently reported that in normal cycling women plasma immunoreactive LH-RH showed a sharp peak 32 h after iv administration of conjugated estrogens during the mid-follicular phase (Miyake et al., 1983). We found that LH was significantly suppressed from 6 h to 42 h after the injection and then showed a rebound increase with a peak at 56 h. The present results are consistent with these previous data.

It has been reported that in hyperprolactinemic patients, the gonadotropin response to clomiphene (Thorner et al., 1974; Bohnet et al., 1976) and LH responses to estrogen (Glass et al., 1975; Aono et al., 1976; L'Hermite et al., 1978) and pulsatile LH secretion (Bohnet et al., 1976) are generally impaired, although tonic secretion of gonadotropin is well maintained (Aono et al., 1976; Bohnet et al., 1976; Healy et al., 1977). This impaired gonadotropin secretion is restored by normalization of the PRL level by bromocriptine treatment (Asfour et al., 1977; Aono et al., 1979) and transsphenoidal surgery to remove prolactinomas (Koike et al., 1982). Hökfelt and Fuxe (1972) ob-
served that PRL causes a dose-dependent increase in the turnover of dopamine in median eminence neurons. Dopamine seems to exert its inhibitory action on LH-RH neurons (Gudelsky et al., 1976; Chatani et al., 1983). From these findings, it has been postulated that hyperprolactinemia may disturb the hypothalamic function involved in the positive feedback effect of estrogen on LH secretion. The present study indicates that sulpiride-induced hyperprolactinemia suppresses the release of both LH-RH and LH after intravenous estrogen administration. These data suggest that the impaired positive feedback effect of estrogen on LH release in anovulatory women with hyperprolactinemia may be caused, at least in part, by disturbed LH-RH release.

It has been reported that an increased level of PRL blocks the action of gonadotropins at the ovarian level (McNatty et al., 1974; Wang et al., 1980), and it is conceivable that inadequate estrogen production by the ovary impairs the positive feedback effect of estrogen on LH release. Indeed, in the present study the estradiol level was found to be lowered significantly by sulpiride administration. Therefore, it is not clear whether the disturbed LH-RH secretion after estrogen injection in hyperprolactinemic women is caused by a direct action of PRL on the hypothalamus or by ovarian dysfunction with inadequate estrogen production. Further studies are necessary to elucidate the precise mechanism of action of PRL on the positive feedback effect of estrogen on LH-RH release.

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References


