Effects of Progesterone on Prolactin Secretion in Hypogonadal Women

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Abstract

Although estrogen is known to stimulate the secretion of prolactin, there are only slight differences between the prolactin levels in the follicular and luteal phases in normal women. To test the hypothesis that progesterone is involved in the regulation of prolactin release, 50mg of progesterone was administered intramuscularly at 0600h to twelve hypogonadal women and blood samples were obtained at 15 min intervals between 1500 and 2000h to determine the prolactin levels. The day before progesterone treatment, control blood samples were obtained at 15 min intervals between 1500 and 2000h. The serum progesterone levels were 28.7±4.1ng/ml at 1500h, 24.2±3.5ng/ml at 1730h and 21.3±2.9ng/ml (mean±SD) at 2000h. In eight of twelve hypogonadal women, progesterone lowered circulating prolactin levels significantly. These results indicate that a high level of progesterone in the luteal phase may partly block estrogen-induced prolactin release physiologically.

It is well known that estrogens raise serum prolactin levels. The differences in prolactin found in men, and women before and after the menopause has been correlated to differences in estrogen production (Vekemans and Robyn 1975, Ehara et al., 1973, Reyes et al., 1977). Several reports dealing with the effects of estrogen medication on prolactin in hypogonadal women (Yen et al., 1974, Robyn and Vekemans 1976, Andersen et al., 1980) and in men (Frantz et al., 1972) showed the marked positive effect of estrogen in secretion of prolactin. On the other hand, estrogens in combination with gestagen administrations caused a slow and modest rise in serum prolactin in hypogonadal women (Hagen et al., 1982) or did not affect the serum level of prolactin in hypogonadal (Lind et al., 1978) as well as in norman women (Davis et al., 1984).

Changes in prolactin levels during the menstrual cycle had been controversial. Some investigators have failed to observe any systemic fluctuation on prolactin levels during the cycle (Ehara et al., 1973, McNeilly and Chard 1974, Epstein et al., 1975), while recent reports, referred to an overall pattern of serum prolactin during the menstrual cycle which resembled that for circulating estradiol (Franchimont et al., 1976, Vekemans et al., 1977, Djursing et al., 1981, Minakami et al., 1985) with small differences between the prolactin levels in the follicular and luteal phases. In addition, relative
hyperestrogenism caused an exaggerated prolactin response of thyrotropin-releasing hormone in women with chronic anovulation (Peillon et al., 1982).

These observations suggest that progesterone may play a role in inhibiting prolactin release in the human luteal phase physiologically. Since the effect of progesterone on prolactin secretion in human beings has not been fully considered, we examined the effect of this steroid in hypogonadal women. Our observation that progesterone has the effect of inhibiting prolactin release in hypogonadal women should help in understanding why serum prolactin fails to rise to the expected level in the human luteal phase and during treatment with estrogens in combination with gestagen.

Subjects and Methods

Ten postmenopausal women who had amenorrhea for at least 3 years and 2 women who were ovariectomized 3 and 5 years ago, between 35–60 yr of age, volunteered for this study. All subjects were in good health and not taking any medicines. Regular meals were provided and the subjects were not permitted to sleep or smoke during the experiments.

Their pretreatment values for serum estradiol and progesterone were all lower than 25.0 pg/ml and 0.5 ng/ml, respectively. On the day before the experiment, blood samples were obtained through

Table 1

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Age</th>
<th>Yrs after menopause or oophorectomy</th>
<th>Mean PRL (ng/ml) ( a )</th>
<th>( \text{pre}^b )</th>
<th>( \text{post}^c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>6</td>
<td>12.5 ± 3.9</td>
<td>7.0 ± 3.2</td>
<td>****</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>5</td>
<td>16.6 ± 4.0</td>
<td>12.4 ± 3.0</td>
<td>***</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>6</td>
<td>8.0 ± 1.7</td>
<td>7.6 ± 2.2</td>
<td>N.S.</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>3</td>
<td>12.8 ± 1.6</td>
<td>12.5 ± 1.6</td>
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</tr>
<tr>
<td>5</td>
<td>59</td>
<td>6</td>
<td>7.2 ± 1.8</td>
<td>5.8 ± 1.8</td>
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<tr>
<td>6</td>
<td>57</td>
<td>9</td>
<td>6.1 ± 1.1</td>
<td>5.5 ± 1.1</td>
<td>N.S.</td>
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<tr>
<td>7</td>
<td>57</td>
<td>5</td>
<td>11.3 ± 2.1</td>
<td>8.2 ± 2.8</td>
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</tr>
<tr>
<td>8</td>
<td>60</td>
<td>5</td>
<td>10.8 ± 1.5</td>
<td>8.4 ± 0.7</td>
<td>****</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>3</td>
<td>17.6 ± 5.5</td>
<td>10.9 ± 1.7</td>
<td>***</td>
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<tr>
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<td>57</td>
<td>4</td>
<td>12.4 ± 1.9</td>
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<td>4</td>
<td>10.0 ± 2.9</td>
<td>8.5 ± 1.2</td>
<td>*</td>
</tr>
<tr>
<td>12</td>
<td>56</td>
<td>9</td>
<td>16.3 ± 2.6</td>
<td>12.8 ± 2.5</td>
<td>***</td>
</tr>
</tbody>
</table>

\( a \) : Mean ± S.D.
\( b \) : before administration of progesterone
\( c \) : after administration of progesterone

\* : Significantly different from a pre-value at \( p < 0.05 \)
\** : Significantly different from a pre-value at \( p < 0.02 \)
\*** : Significantly different from a pre-value at \( p < 0.01 \)
\**** : Significantly different from a pre-value at \( p < 0.001 \)
an indwelling venous catheter between 1500 and 2000 h at 15 min intervals. At 0600 h on the day of the experiment, 50 mg of progesterone was administered intramuscularly. Then blood samples were drawn between 1500 and 2000 h at 15 min intervals.

Serum was obtained by centrifugation within 1 hour after the blood was drawn and was then stored at -15°C until analyzed. Serum prolactin concentration was determined using a double antibody radioimmunoassay kit supplied by Daiichi Radioisotope Lab (Japan). The intra-assay and inter-assay coefficients of variation for prolactin were 6% and 11% respectively.

To minimize the effects of interassay variation, all 42 samples obtained from a single volunteer throughout the entire course of this study were assayed in a single RIA for prolactin.

The results were analyzed by Student’s t-test.

Results

After administration of 50 mg of progesterone intramuscularly at 0600 h, the mean circulating level (±SD) of progesterone reached 28.7±4.1 ng/ml at 1500 h, 24.2±3.5 ng/ml at 1730 h and 21.3±2.9 ng/ml at 2000 h.

In eight of twelve cases, serum prolactin levels were lowered significantly after progesterone treatment. (Table 1) The serum prolactin levels were not suppressed significantly after progesterone treatment in the remaining 4 cases. However, the mean levels of prolactin on the experimental day did not exceed the mean values on the control day. Individual data for the prolactin of eight subjects who had a significantly suppressed serum prolactin level after progesterone treatment are shown in Fig. 1. Episodic fluctuations in the serum prolactin concentration were observed in all cases. However, we could not find any consistent difference between the patterns of episodic prolactin secretion before and after progesterone treatment.

Fig. 2 shows the percentage changes from the mean value (100%) of control day samples in twelve hypogonadal women. At 1500, 1515, 1530, 1545, 1600, 1615, 1630, 1645, 1715, 1800, 1830, 1845, and 1915 h on the day of progesterone treatment, circulating prolactin levels were decreased
Discussion

The present study demonstrates the suppressive effect of progesterone on prolactin release in hypogonadal women. The underlying mechanism(s) accounting for this effect of progesterone is unclear.

Recently, concomitant pulsatile release of prolactin and luteinizing hormone in hypogonadal women (Cetel and Yen 1983) and in normal women (Braund et al., 1984) was reported. Exogenous GnRH stimulates secretion of prolactin in normal men (Van Loon 1978), normal women (Yen et al., 1980, Braund et al., 1984) and in various pathological conditions (Giampietro et al., 1979, Beumont et al., 1980, Georgitis et al., 1983). Furthermore, Gooren et al. (1984) observed the phenomenon that endogenous and exogenous GnRH has a positive effect in releasing prolactin in response to thyrotropin-releasing hormone in men. A similar phenomenon has been observed previously (Spitz et al., 1979). In addition, it has been reported that GnRH stimulated secretion of prolactin in co-cultured female rat lactotropes and gonadotropes (Denef et al., 1982). The simplest interpretation of these data is that endogenous and exogenous GnRH stimulate secretion of prolactin from the pituitary gland. On the other hand, it has been reported that GnRH pulse frequencies could be decreased by progesterone treatment in ovariectomized sheep (Goodman and

![Fig. 2. Effects of progesterone on serum prolactin concentrations in samples obtained at 15-min intervals between 1500 and 2000 h in twelve hypogonadal women. The closed and open circles represent percentage changes from the mean value for prolactin on control day (100%) before and after the administration of progesterone at 0600 h. Vertical bars show SEMs. Asterisks indicate a significant difference between levels at the same time before and after the progesterone treatment. *: p<0.05 **: p<0.02 ***: p<0.01 ****: p<0.001]
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Karsch (1980) and normal women (Soules et al., 1984). We also showed this effects of progesterone in the subjects of the present study (Minakami et al., 1984). It was also demonstrated that after ovariectomy, restoration of luteal phase levels of progesterone markedly attenuated the acute increase in luteinizing hormone release in rats (Leipheimer et al., 1984). This was in response to a decrease in luteinizing hormone pulse amplitude without diminishing the response of the pituitary to GnRH (Leipheimer et al., 1984). These reports indicate that progesterone in the luteal phase may act in the brain to decrease GnRH secretion with prolongation of the GnRH pulse interval in sheep and women or diminishing GnRH pulse amplitude in rats.

These experimental data, together with the suppressive effect of progesterone on prolactin release demonstrated for the first time in our study, may support the hypothesis that the prolonged intervals between GnRH pulses generated by progesterone treatment might cause a reduction in circulating prolactin levels. Additionally, endogenous dopamine may also be involved. In rats, progesterone administered subcutaneously can lead to an increased secretion of dopamine into hypophysial portal blood resulting in a lowering of the prolactin level (Cramer et al., 1979). The report that exogenous GnRH lowered the circulating dopamine level in normal men (Van Loon 1978), supports the theory that a decrease in endogenous GnRH may reciprocally induce or occur with an increase in tuberoinfundibular dopamine release, but direct evidence implicating the GnRH-dopamine relationship in the hypothalamus remains to be produced.

Progestosterone is known to induce gonadotropin release in estrogen-primed hypogonadal women (Nillius and Wide 1971) as well as normally cycling women (Chang and Jaffe 1978), suggesting a physiological role of this steroid at midcycle. Similarly, it is reported that progesterone elicits a prompt pituitary release of prolactin in estrogen-primed normal women during early follicular phase (Rakoff and Yen 1978). This report may explain the finding that the highest serum prolactin level is found at midcycle (Vekemans et al., 1977). These reports, together with our findings, indicate that progesterone has a facilitory effect on prolactin release at midcycle and an inhibitory effect on prolactin release during the luteal phase, as progesterone does on gonadotropin release.

It remains to be demonstrated whether or not progesterone has a direct effect at the lactotrope level. Further studies are needed.

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References


Cramer, O. M., C. R. Parker, Jr. and J. C. Porter...


